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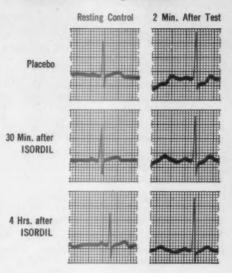
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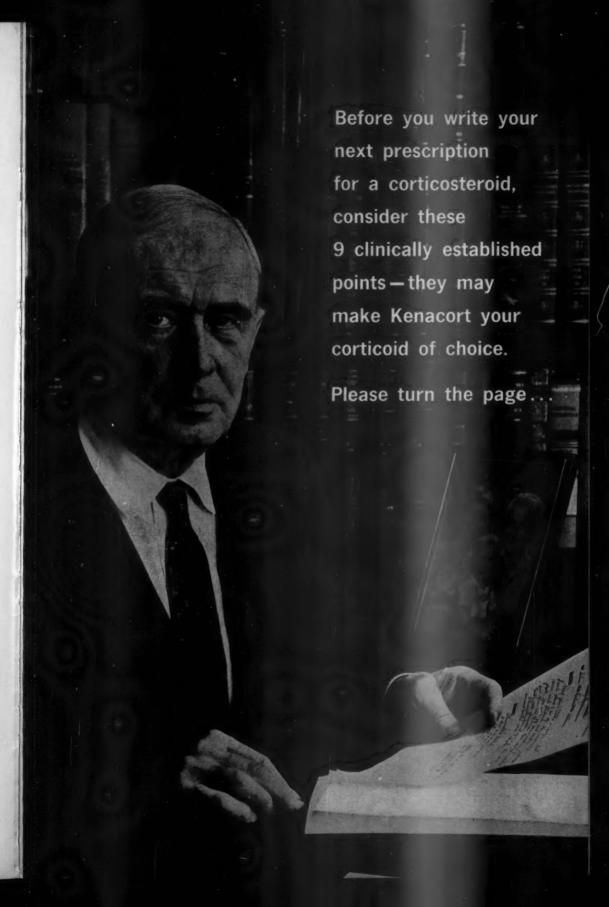
References: 1. Riseman, J.E.F., et al.: Circulation 17:22-39 (Jan.) 1958. 2. Sherber, D.A.: Persona Communication (Oct., 1959). 3. Case Reports on File, Ives-Cameron Company (1958-1959). 4. Summary of Case Reports on File, Ives-Cameron Company (1958-1959). 5. Albert, A.: Personal Communication (Oct., 1959). 6. Russek, H.I.: Personal Communication (Oct., 1959). 7. Harris, E., et al.: Personal Communication (Oct., 1959).





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initial therapy remarkably free from complications

Allison, J. R., Sr., and Allison, J. R., Jr.: Monographs on Therapy 3:99 (Oct.) 1958. pre-prescription point number 4

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Council on Drugs: J. A. M. A. 169:257 (Jan. 17) 1959.

pre-prescription point number 2

continuing therapy
-maintenance doses
are low

Feinberg, S. M.; Feinberg, A. R., and Fisherman, E. W.: J. A. M. A. <u>167</u>:58 (May 3) 1958.

pre-prescription point number 5

less likely to create electrolyte disturbance

Benglovenni, A. M.; Hellman, W. J., and Eberlein, W. R.; J. Pediat. 52:3 (July) 1958.

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J.A. H. A. 167:973 (June 21) 1958.

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no secondary hypertension—no significant change in pulse, respiration, or blood pressure

Shelley, W. B.: Harun, J. S., and Pilisbury, D. M.: J. A. M. A. <u>167</u>:959 (June 21) 1988. Berristen, C. A., Jr., and others: New York Rhouselton, Annual Meeting New York, April 9, 1909.

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J. A. M. A. 169:257 (Jan. 17) 1959.

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Shelley, W. B.; Harun, J. S., and Pilisbury, D. M.; J. A. M. A. <u>167</u>:959 (June 21) 1958. Council on Drugs: J. A. M. A. <u>169</u>:257 (Jan. 17) 1959.

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J. A. M. A. 167:973 (June 21) 1958.



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*Thompson, R. E., and Hecht, R. A.: Am. J. Clin. Nutrition 7:311-317 (May-June) 1959.

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Orbach, E. J.: J. Internat. Coll. Surgeons 31:165, 1959.

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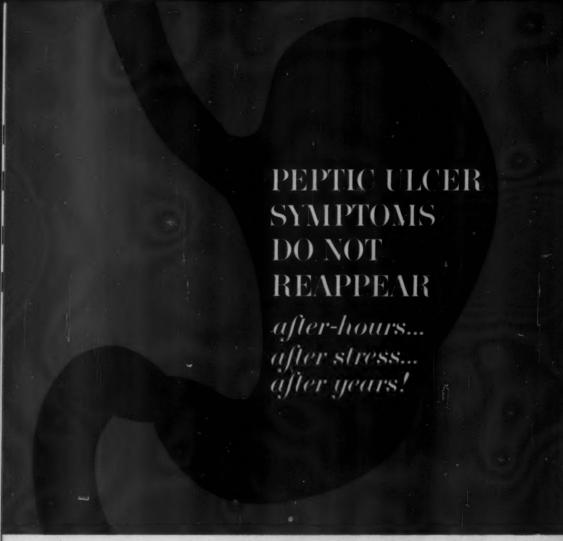
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1. Seizer, A. and Rytand, D.A.: COUNCIL ON DRUGS, Report to Council J.A.M.A. 169:762, (Oct. 11) 1958.





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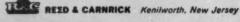
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SUPPLIED: Bottles of 50 and 100 tablets.

CONTRAINDICATIONS: Contraindicated in glaucoma because of its anticholinergic components.

Rosenblum, L. A.: Report, Symposium on Peptic Ulcer, University of Vermont School of Medicine, September 24, 1959.

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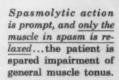
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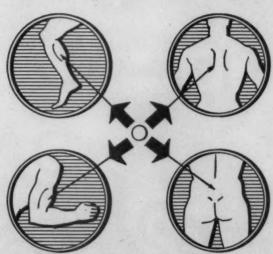


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Kotkov, B.. Group psychotherapy with the obese. Paper read before The Academy of Psychosomatic Medicine, October 1958.



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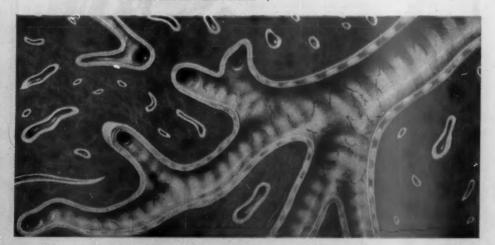


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now in oral, parenteral, and suppository forms effective but not "side effective"

Tigan blocks emetic impulses at the chemoreceptor trigger zone (CTZ),1 a medullary structure activating the vomiting center. While Tigan shares with the phenothiazines the mode of antiemetic action, this is their only similarity.1 In extensive clinical studies2-14 Tigan, unsurpassed in specificity, has exhibited a virtually complete absence of side effects. Tigan has demonstrated no sedative or tranquilizing properties, no hypotensive or supramedullary effects, no extrapyramidal tract stimu-



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in nausea/vomiting
of pregnancy

No evidence of sedation or other side effects¹² observed in a series of patients of whom 94 per cent became asymptomatic on Tigan. On other antiemetic medication, several had failed to respond or had complained of drowsiness.¹²

in nausea/vomiting of radiation sickness

Protected with Tigan "... not one patient had to discontinue [deep radiation] treatments..."

in nausea/vomiting of drug administration "...large intermittent dose[s] of [nitrogen mustard and other drug] therapy could be given without the associated nausea and vomiting that we had seen before."

118311 specific antiemetic antinauseant

no sedative properties no tranquilizer side effects

Suggested uses: Both prophylactic and therapeutic control of nausea and vomiting associated with pregnancy, travel sickness, gastrointestinal disorders, operative procedures, carcinomatoses, toxicoses, other underlying disease processes, drug administration and radiation therapy.

Dosage: Adults — 1 or 2 capsules, orally, 2 cc intramuscularly, q.i.d. or 1 suppository, q.i.d. For children's dosage, consult literature.

In nausea and vomiting of pregnancy — Satisfactory control is usually achieved with an initial dose of two capsules immediately upon awakening. If possible, the patient should remain in bed for one-half to one hour following this dose. When nausea and vomiting are not confined to the morning hours, supplemental doses of one or two capsules should be given throughout the day at intervals of three to four hours.

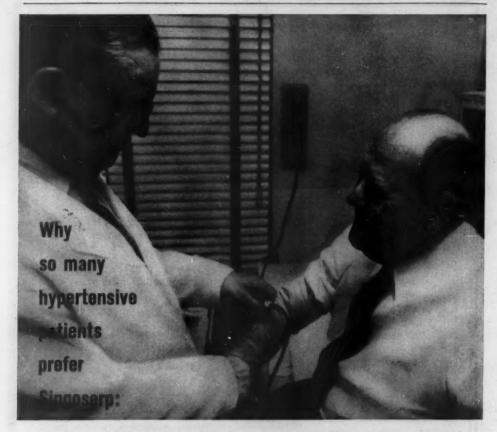
How Supplied: Tigan capsules, 100 mg, blue and white—bottles of 100 and 500. Tigan ampuls, 2 cc (100 mg/cc)—boxes of 6 and 25. Tigan Pediatric Suppositories, 200 mg, boxes of 6.

References: 1. W. Schallek, G. A. Heise, E. F. Keith and R. E. Bagdon, J. Pharmacol. & Exper. Therap., 126:270, 1959. 2. W. B. Abrams, I. Rosefi, J. Kaufman, L. Goldman and A. Bernstein, to be published. 3. I. Rosefi, W. B. Abrams, J. Kaufman, L. Goldman and A. Bernstein, J. Newark Beth Israel Hosp., 9:189, 1958. 4. O. C. Brandman, paper read at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. 5. J. A. Lucinian, ibid. 6. D. W. Molander, ibid. 7. B. I. Shnider, ibid. 8. W. S. Derrick, ibid. 9. B. Wolfson and F. F. Foldes, ibid. 10. McLaughlin, ibid. 11. Reports on file, Roche Laboratories. 12. Personal communications. 13. W. K. Gauthier, Discussant at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. 14. H. E. Davis, ibid.

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*Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. 169:1609 (April 4) 1959.



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By-Effects of Three Other Ganglionic-Blocking Agents^{6,7,8} Compared with Those of Ostensin^{1,9}

| | Other Agents | OSTENSIN |
|----------------------|--------------------|-----------------|
| Constipation | 59-69% of patients | 5% of patients |
| Postural hypotension | 33-59% of patients | 37% of patients |
| Visual disturbances | 42-50% of patients | 34% of patients |
| Dry mouth | 38-41% of patients | 15% of patients |

"Of particular interest has been the virtual absence of constipation despite adequate blood pressure control. This finding suggests a lower risk of paralytic ileus...."

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1. Dunsmore, R.A., et al.: Am. J. M. Sc. 236:483 (Oct.) 1958. 2. Blaquier, P., et al.: Univ. Michigan M. Bull. 24:409 (Oct.) 1958. 3. Smirk, F.H.: Submitted for publication. 4. Janney, J.F.: Submitted for publication. 5. Council on Drugs, A.M.A.: J.A.M.A. 166:640 (Feb. 8) 1958. 6. Freis, E.D., and Wilson, I.M.: Circulation 13:856 (June) 1956. 7. Moyer, J.H., et al.: A.M.A. Arch. Int. Med. 98:187 (Aug.) 1956. 8. Moyer, J.H., et al.: Am. Pract. & Dig. Treat. 7:1765 (Nov.) 1956. 9. Dunsmore, R.A. In Tislow, R.F., et al.: Scientific Exhibit. Presented at Annual Convention of A.M.A., San Francisco, June 23-27, 1958.



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References: 1. Cronk, G.A.; Naumann, D.E., and Casson, K.: Antibiotic Annual 1937-1938, New York, Medical Encyclopedia Inc., 1938, p. 397. 2. Childs A.J.; Brit. M.J. 1:660 (Mar.) 1956. 3. Newconer, V.D.; Wright, E.T., ans Sternberg, T.H.: Antibiotics Annual 1934-1935, New York, Medical Encyclopedia Inc., 1935, p. 666. 4. Gimble, A.I.; Shea, J.G., and Katz, S.: Antibiotics Annual 1935-1956, New York, Medical Encyclopedia Inc., 1936, p. 676. 5. Stone, M.L. and Mersheimer, W.L.: Antibiotics Annual 1955-1954, New York, Medical Encyclopedia Inc., 1956, p. 862. 6. Campbell, E.A.; Prigot, A., and Dorsey, G.M.: Antibiotic Med. & Cilia. There, 4:817 (Dec.) 1937.

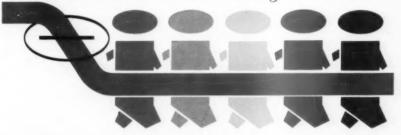
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Radding, R. S.: Texas J. Med. 55:110, 1959.

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167:675 (June 7) 1958.

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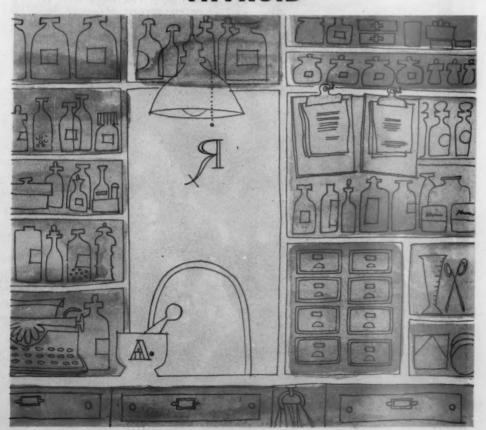
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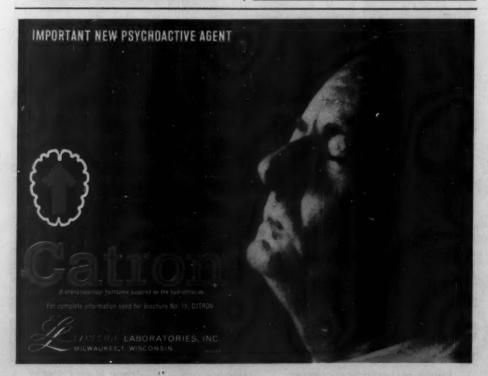
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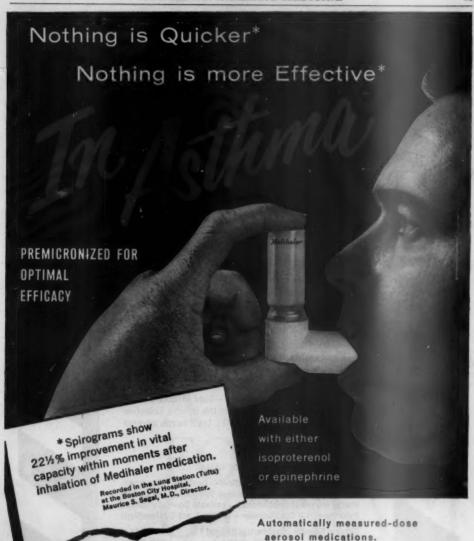
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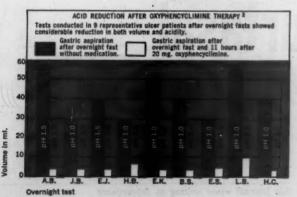
Supplied: in bottles of 60 black-and-white scored tablets.



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Réferences: 1. Steigmann, F.: Study conducted at Cook County Hospital, Chicago, Illinois: in press. 2. Winkelstein, A.: Am. J. Gastroenterol. 32:66 (July) 1959. 3. Data in Roerig Medical Department files. 4. Leming, B. H., Jr.: Clin, Med. 8:423 (Mar.) 1959.



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1. Doshay, L. J. et al. J.A.M.A. 160:348 (Feb.) 1956. 2. Berris, H.: T. Lancet 74:245 (July) 1954.

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*Records of Medical Department, Abbott Laboratories, North Chicago, Illinois

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Its two components, and B, have been isola line state from the ferr of a new species of Nocardia lurida. Bot are active against gra teria and mycobacter mycete was isolated f ple collected from th Gods, Colorado Sp No other culture wh same antibiotic has

The chemical cha ristocetins are not co though they are kno teric substances con phenolic groups ristocetin A and ris molecules with me the vicinity of 4000 have good stability pH range of bloc SPONTIN is a ly tion, derived fr material, represe ristocetins A ar

Antimicrobial tion against gra ganisms, SPON effective than able antibiotics

Against pne cocci (except s cocci) the antil tericidal at th concentration hibits the gro also kills ther

This obse for the majo lococci. Ho staphylococ have been to centration : minimum i produce a this reason SPONTIN for the trea

and enterococcal infections.

Cultures of staphylococcus aureus, which are resistant to other antibiotics have been shown to be sensitive to Spontin. There has been no case reported in which a staphylococcal or enterococcal strain has exhibited a

tion, derived from pure crystalline material, representing a mixture of ristocetins A and B.

Antimicrobial Properties. In its action against gram-positive coccal or-SPONTIN is notably more ntly avail-

Summary and Conclusions

Major use has been treating staphylococcic infections. Of the total 333 cases, approximately one-third was treated for pneumonia; of these over 80% were either cured or improved. About 70% of these pneumonias were caused by staphylococci.

The next largest group included 46 patients with subacute bacterial endocarditis. About 50% of these infections were identified as staphylococcic and a further 15% as enterococcic. Other infections included 38 cases of septicemia, 32 abscesses and 24 patients with osteomyelitis.

The administration of SPONTIN brought about a cure in 60% of all the cases reviewed and improvement in a further 17%.

Side-effects were seldom troublesome when a daily dose of 2 Gm. was not exceeded. The incidence rose as the dosage was increased. The most disturbing side-effect after administration of Spontin has been neutropenia. However, in all instances this has responded to either discontinuance of medication or reduction in dose.

d streptoof enteroiably bacage. The which inorganisms

holds true of staphystrains of cocci which uired a conher than the centration to ffect. It is for er dosage of recommended taphylococcal tions.

occus aureus. other antibito be sensitive been no case phylococcal or as exhibited a SPONTIN.

that the antibi-TIN is enhanced amma globulin. supported by the ivo activity of nes greater than from the in vitro

stigators* have recal response followration of SPONTIN dies have shown a ity on the part of anism. Satisfactory may be expected m requires up to 25 NTIN for inhibition llowing table shows sitivities of different major pathogenic

pH range of bio SPONTIN is a lyophilized prepara-

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"When chlorothiazide is used, lower and, hence, less toxic dosages of other antihypertensive agents become effective in controlling blood pressure. Chlorothiazide does not reduce blood pressure in normotensive subjects, although the drug induces the same increase in salt excretion."

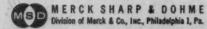
Freis, E.D.: J.A.M.A. 188:105, (Jan. 10) 1959.

Desage: One 250 mg. tablet DIURIL b.i.d. to one 500 mg. tablet DIURIL t.i.d.

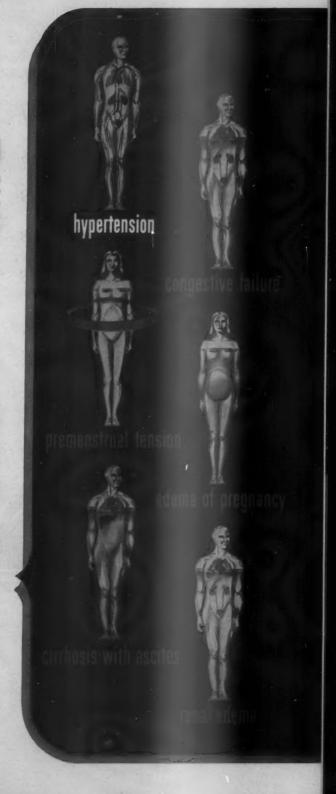
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Exhibits unusual analgesic properties, different from those

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supplied: Bottles of 50 white sugar-coated 350 mg. tablets. Literature and samples on request.



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The speed of action and reliability of oral potassium penicillin V have been dramatically demonstrated by recent studies^{1,2} in which 107 subjects were each given 400,000 units of the antibiotic. Appreciable penicillin levels were consistently produced within 15 minutes; peak levels within one-half hour. Penicillin levels still persisted in all subjects at two hours, and in 93 per cent of subjects at four hours.

1. Peck, F.B., Jr., and Griffith, R.S.: Antibiotics Annual 1957-1958, Medical Encyclopedia, Inc., p. 1004. 2. Wright, W.W., and Welch, H.: Antibiotic Med. 5:139 (Feb.) 1958. PEN-VEE K

Liquid: Penicillin V Potassium for Oral Solution; Philadelphia 1, P. Tablets: Penicillin V Potassium, Wyeth

SUPPLIED: Liquid: raspberry-flavored, 125 mg. (200,000 units) per 5-cc. teaspoonful; peach-flavored, 250 mg. (400,000 units) per 5-cc. teaspoonful. Both supplied as vials of powder to make 40 cc. Tablets: 125 mg. (200,000 units) and 250 mg. (400,000 units) in vials of 36.

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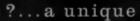


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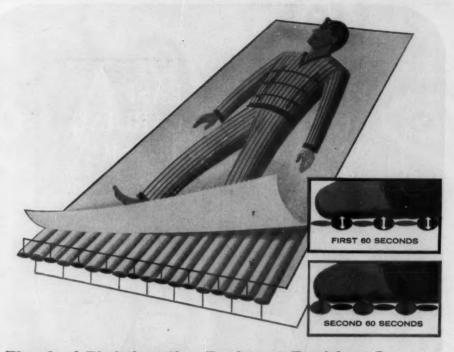
For convenience, write "CARTRAX 10" or "CARTRAX 20."

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References: 1. Russek, H. I.: Postgrad. Med. 19:562 (June) 1956. 2. Russek, H. I.: Presented at the Symposium on the Management of Cardiovascular Problems of the Aged, Dade County Medical Association, Miami Beach, April 12, 1966.



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Bibliography: (1) N. Raiph, Am. J. M. Sc. 227:297, 1954. (2) H. A. Bickerman, in W. Modell, Ed., Drugs of Choice 1958-1959, St. Louis, The C. V. Mosby Company, p. 557. (3) H. A. Bickerman, E. German, B. M. Cohen and S. Itkin, Am. J. M. Sc. 234:191, 1957. (4) L. J. Cass, W. S. Frederik and J. B. Andosca, Am. J. M. Sc. 227:291, 1954. (5) L. J. Cass and W. S. Frederik, J. Lab. & Clin. Med. 48:879, 1956. (6) L. J. Cass and W. S. Frederik, New England J. Med. 249:132, 1953. (7) H. Isbell and H. F. Fraser, J. Pharmacol. & Exper. Therap. 107:524, 1953. (8) W. M. Benson, P. L. Stefko and L. O. Randall, J. Pharmacol. & Exper. Therap. 109:189, 1953. (9) New and Nonofficial Drugs 1959, Philadelphia, J. B. Lippincott Company, p. 326.

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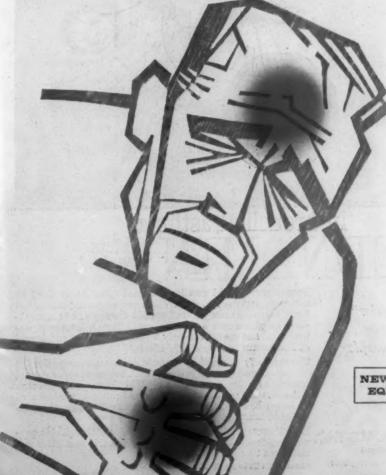
1. Russek, H.I.: Am. J. Cardiol, 3:547 (April) 1959.

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*Swartz, H.: To be published.



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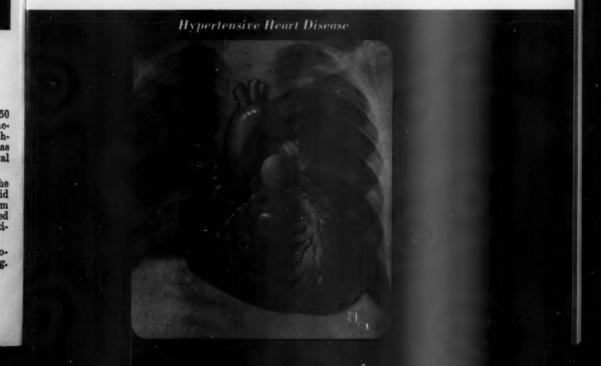
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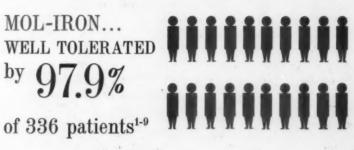
*BATTERMAN, R. C., ET AL.: CIRCULATION 5:201, 1982
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References: 1. Shelmire, J.B., Jr.: Monographs on Therapy 3:164 (Nov.) 1958. • 2. Nix, T.E., Jr., and Derbex, V.J.:
Monographs on Therapy 3:123 (Nov.) 1958. • 3. Robinson, R.C.V.: Butl. School of Med, U. Maryiand 43:54 (July)
1958. • 4. Sternberg, T.H.: Newcomer, V.D., and Reisner, R.M.: Monographs on Therapy 3:115 (Nov.) 1958. • 5.
Clark, R.F., and Hallett, J.J.: Monographs on Therapy, 3:153 (Nov.) 1958. • 6. Smith J.G., j.; Zawisza, R.J., and Hallett, J.J.: Monographs on Therapy, 3:153 (Nov.) 1958. • 7. Monographs on Therapy, 3:137 (Nov.) 1958. • 8.
Howell, C.M., Jr.: North Carolina M.J. 19:449 (Oct.) 1958. • 9. Bereston, E.S.: South, M.J. 50:547 (April) 1958. • 8.
Howell, C.M., Jr.: North Carolina M.J. 19:449 (Oct.) 1958. • 9. Bereston, E.S.: South, M.J. 50:547 (April) 1959. • 8.
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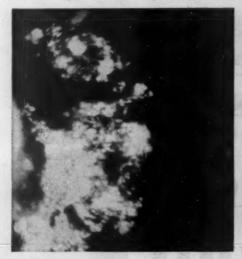
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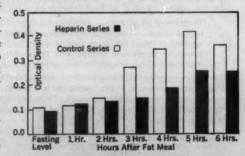
Dosage: After each meal, hold one tablet under the tongue until dissolved.

Supplied: In bottles of 50 pink, sublingual tablets, each containing 1500 I.U. heparin potassium.

- 1. Fuller, H. L.: Angiology 9:311 (Oct.) 1958.
- Shaftel, H. E., and Selman, D.: Angiology 10:131 (June) 1959.



WITH CLARIN, clear blood serum five hours after a fat meal: After eating a standard fat meal as at left, the same patient has taken one sublingual Clarin tablet. Note marked clearing effect and reduction in massive fat concentrations in this unretouched photomicrograph (2500X).



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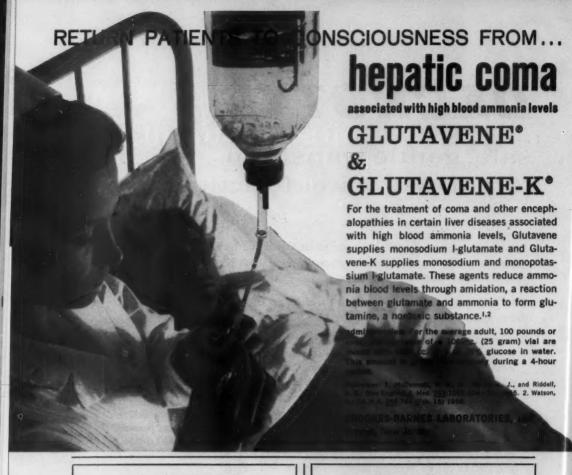
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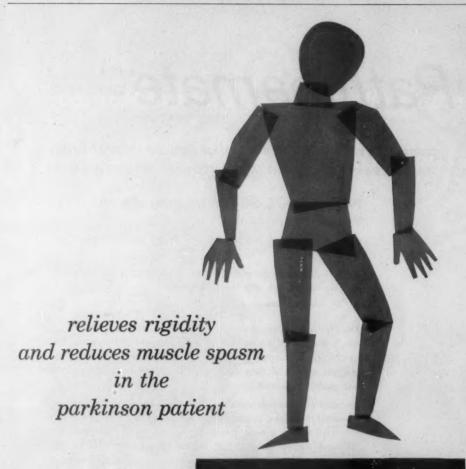
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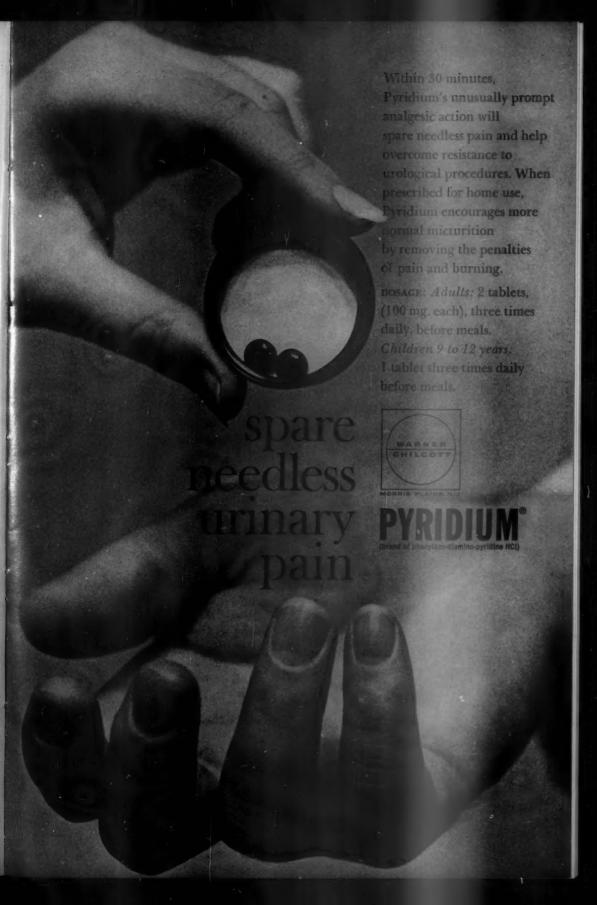
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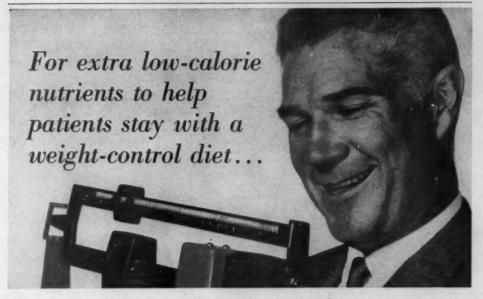
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*Doshay, L. J., and Constable, K.: Treatment of Paralysis Agitans with Chlorphenoxamine Hydrochloride, J.A.M.A. 170:37 (May 2) 1959.

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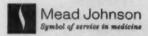
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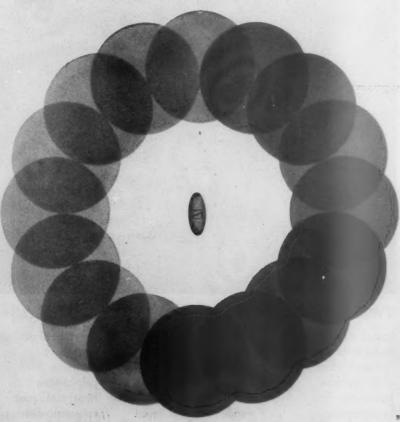
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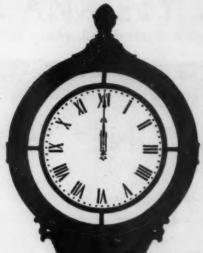
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ORAL ANTIDIABETIC THERAPY * †

By ROBERT H. WILLIAMS, M.D., F.A.C.P., RICHARD H. POLLEN, M.D., Seattle, Washington, Donald C. Tanner, M.D., Bellevue, Washington, and ROBERT H. BARNES, M.D., Seattle, Washington

THERE is some evidence suggesting that the majority of patients with diabetes have subnormal concentrations of insulin in the plasma, but a hypernormal quantity of insulin has been demonstrated in certain instances. Insulin administration has proved to be of tremendous value, especially in those types of diabetes which seem to be associated with subnormal amounts of this hormone, for example, juvenile diabetes. Nevertheless, almost all of the juvenile diabetics develop one or more of the chronic complications of diabetes (retinopathy, intercapillary glomerulosclerosis, etc.) within an interval of 20 years, regardless of ardent efforts by the patients and their physicians to avoid such. There are suggestions that the complications may result from abnormalities in lipid and protein metabolism occurring during the several hours of numerous days when insufficient insulin is available. Efforts to provide insulin action throughout 24-hour intervals have often led to hypoglycemic reactions, sometimes producing permanent brain damage and, occasionally, death. Vigorous search for orally effective compounds has been made in an effort to attain smoother control of diabetes, especially with greater convenience. Numerous compounds have been tested, but four

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From the Department of Medicine, University of Washington School of Medicine, Seattle, Washington.

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With the assistance of Fred T. Darvill, M.D., Mount Vernon, Washington, William H. Stimson, M.D., Howard M. Hackedorn, M.D., Sydney Weinstein, M.D., and William J. Kelly, M.D., Seattle, Washington.

Requests for reprints should be addressed to Robert H. Williams, M.D., Department of Medicine, University of Washington, Seattle 5, Washington.

are receiving greatest attention at present: tolbutamide, chlorpropamide, metahexamide and phenethylbiguanide. Since there have been numerous publications and symposia 1-16 relative to these compounds, little information on the early investigations of them will be presented here, but a report of their present status is recorded. In this brief summarization no effort is made to refer to the vast literature relative to most of the individual statements made, but information pertaining thereto is found in the references listed.

SULFONYLUREAS

As seen in figure 1, tolbutamide, chlorpropamide and metahexamide are sulfonamides (SO₂NH₂ grouping) and sulfonylureas (SO₂-urea group-

TOLBUTAMIDE

CHLORPROPAMIDE

Fig. 1. Sulfonylureas used most commonly at present; these compounds are also sulfonamides.

The differences in structure of the side radicals are to be noted.

ing); their blood-sugar-lowering capacity is vested in these groupings. Although the side chains modify the metabolism, potency and side-effects of these compounds, they have many characteristics in common. Since tolbutamide has been investigated much more extensively than the others, particularly as to its mechanism of action, it will be discussed in greater detail.

Tolbutamide

Mechanism of Action: In spite of extensive investigations, universal consensus relative to the mechanism(s) by which tolbutamide lowers the blood

sugar is lacking. However, with all of the observations in mind, the actions diagrammed in figure 2 seem likely. Tolbutamide's major action presumably is to increase insulin release from the pancreatic β cells, but this drug also decreases hepatic glucogenesis, particularly when insulin is present. The following observations suggest that there is increased insulin release:

1. Some investigators have found that tolbutamide increases significantly the quantity of assayable insulin in the plasma.

2. The drug decreases the granules of the β cells and decreases the assayable insulin in the pancreas.

3. An amount of the compound too small to produce hypoglycemia when injected into the femoral vein or portal vein causes marked hypoglycemia when infused into a pancreatic artery.

4. In cross-circulation experiments the recipient animal, whether normal or diabetic, develops hypoglycemia when he receives his blood supply directly from a pancreatic vein of a tolbutamide-treated intact animal, but not when the blood is received from a mesenteric vein or femoral vein.

5. Without exogenous insulin, active β cell function is necessary for hypoglycemic response to the sulfonylureas; totally departreatized animals, or patients, and animals with severe alloxan diabetes fail to respond.

Although tolbutamide in large doses inhibits insulin degradation by liver, there is evidence suggesting that, with the usual therapeutic doses, this action is insignificant.

Tolbutamide usually does not cause an increase in glucose uptake when incubated with muscle or when administered to animals eviscerated, depancreatized or severely alloxanized, but in the presence of actively functioning β cells it increases glucose oxidation and A-V glucose difference.

The increased release of insulin produced by tolbutamide is apparently

SUGGESTED ACTIONS OF TOLBUTAMIDE

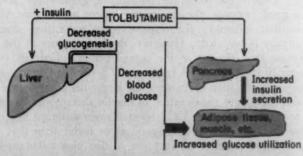


Fig. 2. The major action of tolbutamides presumably is to increase insulin secretion, thereby increasing glucose uptake and utilization by peripheral tissues. Tolbutamide, along with insulin, decreases hepatic glucogenesis. Apparently the blood glucose decreases as a result of increased glucose transfer to tissues and of decreased glucose from the liver.

of only slight magnitude but extends over many hours. This compound, like very small doses of insulin infused into the portal vein, or injected subcutaneously, causes hypoglycemia and decreases hepatic glucogenesis. Tolbutamide produces comparable hypoglycemia in hepatectomized and in intact animals, but it must have a direct action on the liver, because it supplements the hepatic hypoglucogenesis caused by insulin in depancreatized but not in hepatectomized animals. Ordinarily, the direct hepatic effect of tolbutamide seems to be too weak to produce hypoglycemia without the

permissive role of insulin.

Effect on Diabetes: Early investigations with tolbutamide demonstrated that a good response was favored by (a) old age, (b) recent onset of diabetes, (c) small insulin requirements, and (d) other features influencing the type and severity of diabetes. It seems likely that the influence of these factors depends chiefly upon the extent to which they influence insulin secretion and effectiveness. Subjects who develop diabetes before adulthood tend to have progressively less insulin in the pancreas and plasma, with increased duration of the disease, and therefore require increasing quantities of exogenous insulin. Moreover, their β cells presumably become progressively less responsive to tolbutamide. Conversely, the older the individual at the onset of diabetes, apparently the less impaired is β cell activity and the more responsive it is to tolbutamide.

The following comments are based predominantly upon our own experience in the treatment of approximately 200 patients, O'Donovan's survey of data on 9,168 subjects studied by 420 physicians,¹⁷ and the report by

Mehnert et al. dealing with 1,030 diabetics. 18

Approximately two thirds of the diabetics receive a daily maintenance dose of 0.5 to 1.5 gm.; 90% receive 2 gm. or less. Rarely is a dose in excess of 1.5 gm. advantageous; the minimal effective dosage should be sought in all instances. Because of the short half-life of the compound, it is desirable to administer it twice daily—before breakfast and supper.

Although usually the older the patient the greater the possibility of obtaining a good response, the age of the patient at the time his diabetes becomes manifest influences the responsiveness more than does the age at which therapy is initiated. However, the basic nature of the disease is more important than the age of the patient per se. Females, particularly those between 20 and 40 years of age, respond better than do males.

The longer the duration of diabetes, the larger the prior dosage of insulin required; and the longer the duration of insulin therapy, the poorer are the responses to tolbutamide. In 5,233 selected cases analyzed by O'Donovan, the response to tolbutamide was as good as or better than that to insulin. Moreover, in 2,159 patients the response to diet plus tolbutamide was far better than that to diet alone. Many more of the patients would have shown a good response to diet alone had they followed the prescribed diet carefully, but the important point is that they had been given this opportunity pre-

viously. Moreover, there probably was an even smaller proportion who dieted properly while taking drug therapy. Nevertheless, dietary control should be encouraged at all times.

The aforementioned factors are helpful in selecting those patients most likely to respond to tolbutamide therapy. Another helpful measure is an acute screening test. With the administration of a large dose of tolbutamide, orally or intravenously, normals and those diabetics who will experience a good therapeutic response show a marked drop in blood sugar. Mehnert et al., 18 in conducting more than 500 screening tests, concluded that tolbutamide therapy is more likely to be successful the more nearly the test dose reduces the fasting blood sugar to normal. The test is more helpful in designating those patients who will not have a response to long-term therapy than those who will.

Such a test dose is useful in diagnosing diabetes. For example, Unger and Madison 10 found that 20 minutes after its intravenous administration the glucose level of 94% of diabetics remained at 84% or more of the pretest value, whereas in 96% of nondiabetics it had fallen to 80% or less of the pretest values.

The incidence of successful responses to tolbutamide therapy depends upon the type of cases selected for therapy; there have been varying degrees of selection by different investigators. We have obtained good or excellent control in approximately two thirds of our patients. The experiences of Mehnert et. al. 18 were comparable. Approximately 2 to 5% of the patients who show a satisfactory response to tolbutamide for intervals of months subsequently develop a refractoriness to this drug and are said to have "secondary failure." Such a failure is apparently related to the increased capacity of the body to inactivate the compound, rather than to refractoriness to it by the β cells, because the latter often respond to another sulfonylurea and, after omission of the tolbutamide for several months, will again respond to it.

There is no evidence of exhaustion of β cells by prolonged tolbutamide treatment. Indeed, there is more suggestion of an opposite effect, i.e. antidiabetic action. There is a lower incidence of diabetes when partially depancreatized animals are treated with this compound.

Side-Effects: In our experience, significant side-effects from tolbutamide have not occurred during treatment of approximately 200 patients, even though the patients have been examined at frequent intervals for one year or longer. Liver function tests and urine examinations have been repeated in most of the subjects. In his review of 9,168 case reports O'Donovan 17 found side-effects in 3.2%; with withdrawal of the drug, in 1.5%. Mehnert et al.18 noted side-effects in 1.1% of 772 patients. The side-effects have been relatively mild, consisting of headache, malaise, anorexia, epigastric discomfort, diarrhea, skin rashes, leukopenia and hypoglycemia. There are no reports of definite damage to the liver or kidneys.

Comparisons of Chlorpropamide, Metahexamide and Tolbutamide

Metabolism: Metahexamide is absorbed most rapidly from the gastro-intestinal tract; next is chlorpropamide, and then tolbutamide. The half-life of the compounds is as follows: tolbutamide, five hours; metahexamide, 28 hours; chlorpropamide, 36 hours. The major excretory product of tolbutamide in the urine is butyl-p-carboxy-phenylsulfonylurea; this compound results from oxidation of the methyl to a carboxyl group. Chlorpropamide is excreted partially unchanged. About one third of metahexamide is excreted unchanged; presumably the remainder is hydrolyzed, the principal decomposition product being 3-amino-4-methylbenzenesulfonamide. With equal doses, chlorpropamide accumulates most in the body; next is metahexamide, and then tolbutamide.

Blood Sugar Lowering Action: Various investigators have found the blood sugar lowering action of chlorpropamide to be between two and 10 times greater than that of tolbutamide, and that of metahexamide between five and 40 times greater than that of tolbutamide. The differences in these relative potencies should be recalled in attempting to evaluate maintenance doses. With most patients, it is our policy to give as daily maintenance doses 100 mg. of metahexamide, or 250 to 500 mg. of chlorpropamide, in a single dose before breakfast.

Apparently the effective plasma drug level for tolbutamide and chlorpropamide is between 10 and 15 mg. %, while that for metahexamide is between 1 and 5 mg. %. The mechanism of action of chlorpropamide and metahexamide has been studied much less than that of tolbutamide, but presumably the actions of each are similar. Metahexamide, like tolbutamide, has been found to increase the insulin concentration in plasma of nondiabetics and of sulfonylurea-responsive diabetics.

Results with Chlorpropamide in Diabetics: Chlorpropamide and meta-hexamide have been somewhat more effective than has tolbutamide in controlling diabetes. We have encountered successful response to chlorpropamide in 71 of 98 diabetics (72%). Factors which favored a good response were all those that influenced tolbutamide responses. Twenty-four of the 71 chlorpropamide-responsive patients had received tolbutamide: four had had primary failure, 10 had had secondary failure, five had better control on chlorpropamide, and five had excellent control with each drug. Two subjects developed secondary failure to chlorpropamide. Six of 27 patients with unsatisfactory response to chlorpropamide had received tolbutamide: one had had good control, one had had primary failure, and four had had secondary failure.

In analyzing data collected from many investigators, Iezzoni ²⁰ found that in approximately 1,700 patients over 40 years of age, treatment with chlor-propamide produced a good or fair response in 86% and failure in the remainder. Good responses were obtained with chlorpropamide in approximately 60% of those who had primary failure with tolbutamide, and in 80%

of those who had secondary failure. About 0.1% have had secondary failure to chlorpropamide; some of these have responded to tolbutamide and/or metahexamide.

Side-effects from chlorpropamide were found by Iezzoni 20 to occur in approximately 8% of 5,000 patients treated by many physicians; in approximately 3% the drug was discontinued because of side-effects. Anorexia and nausea occurred most frequently; some form of gastrointestinal disturbance was found in 2%. Jaundice was observed in 0.4%; two patients died with jaundice, but it is possible that there were other contributory factors. Some of the jaundiced subjects subsequently received tolbutamide without apparent difficulty, and thereafter, chlorpropamide (in lower doses than formerly). Approximately 3% developed maculopapular or urticarial rashes; three patients developed exfoliative dermatitis, which cleared with cessation of the drug treatment. Mild neurologic disturbances were found in 1.5%. Leukopenia occurred in 0.6%, but there was no agranulocytosis. One patient developed thrombocytopenic purpura, which cleared with cessation of this drug and with administration of corticosteroid therapy.

Results with Metahexamide in Diabetics: Thirty-eight of 77 patients whom we have treated with metahexamide have not responded sufficiently well. However, 20 of these had had unsatisfactory responses to tolbutamide and/or chlorpropamide. When this group is omitted, the incidence of satisfactory response is 68%. Some subjects who failed to respond to other sulfonylureas responded to metahexamide, and vice versa.

We have encountered side-effects from metahexamide in five of our patients: two had mild nausea, one had severe nausea and vomiting, and two had general malaise. Kirtley,²¹ in analyzing data on 3,068 patients treated by 185 physicians, found side-effects in approximately 5%. Nausea and/or vomiting occurred in 5%; headache, dizziness or drowsiness in 0.4%; skin rash in 1%; drug fever in 0.2%; leukopenia in 0.1%. The most important side-effect has been jaundice, which occurred in 0.8%. In most patients the jaundice rapidly subsided upon cessation of therapy. In analyzing the side-effects in 883 diabetics treated by many physicians, O'Donovan ²² concluded that metahexamide should not be used therapeutically.

Comparative Evaluation of Tolbutamide, Chlorpropamide and Metahexamide in the Treatment of Diabetes

The foregoing considerations suggest that tolbutamide should probably be utilized in the treatment of many diabetics, particularly those over the age of 40 with mild disease. Whereas chlorpropamide has a more potent blood sugar lowering effect than does tolbutamide, and metahexamide is more potent than either of the others, the advantages of using chlorpropamide and metahexamide extensively in diabetes do not appear to overbalance the disadvantages that they have exhibited, viz., the greater frequency and

severity of side-effects. Nevertheless, chlorpropamide has advantages in treating certain patients in whom tolbutamide has failed; metahexamide has caused jaundice with sufficient frequency to prohibit further use in the United States. It is clearly evident that, within certain ranges, the incidence of side-effects correlates with the potency of the dosage, and that, compared with tolbutamide dosages, many patients have been treated with much higher effective quantities of chlorpropamide and metahexamide. This error must be corrected before optimal figures relative to side-effects can be obtained.

Chlorpropamide has been found to produce jaundice, apparently by promoting cholestasis. Pericholangitis, as well as cholestasis, has been observed following metahexamide therapy. Relatively little hepatocellular damage has been observed with either drug. The jaundice has usually subsided upon cessation of the drug therapy. Tolbutamide has not been found definitely to have produced jaundice in any patient. All three compounds have been found occasionally to produce hypoglycemia; chlorpropamide and metahexamide have been offenders more often than tolbutamide has. This is apparently due to the use of relatively larger doses of the former two compounds, as well as to their more prolonged action. Symptoms simulating mild hypoglycemic reactions have been observed, in the absence of hypoglycemia, with all three of these drugs, and apparently are due to direct effects of the compounds on the central nervous system; chlorpropamide has been an offender more often than the others have

The sulfonylureas are rarely useful in the treatment of juvenile diabetes, except in some patients, when one is combined with insulin to provide smoother regulation. A patient with unstable diabetes, upon substitution of sulfonylurea for insulin, may develop severe diabetic keto-acidosis and die within one or two days. Sulfonylureas are not very useful during acute stresses. Many patients who are allergic to insulin must be desensitized and treated with this hormone, even though sulfonylureas may ordinarily control their hyperglycemia.

When the daily requirement for insulin is less than 30 units, the insulin may be abruptly replaced by sulfonylurea therapy; otherwise, the transition should be gradual. Especially during the first week, the patient should watch his urine very carefully. Within a week, and certainly within three weeks, it is usually possible to evaluate the effectiveness of this oral type of therapy.

PHENETHYLBIGUANIDE

Guanidine and many of its derivatives have long been known to produce hypoglycemia, but interest has recently been centered on a condensed diguanidine, phenethylbiguanide (PEBG), formula for which is shown in figure 3.

Mechanism of Action: Though many studies reviewed recently 28 have dealt with the mechanism of action of PEBG, information relative to its

Fig. 3.

primary action is incomplete. It inhibits oxidative phosphorylation, and this may cause anoxia; conversely, anoxia inhibits oxidative phosphorylation. PEBG inhibits mitochondrial oxidation, attributable to inhibition of certain oxidative enzymes (e.g., cytochrome oxidase, succinic dehydrogenase). The ensuing anoxia may lead to hypoglycemia through two mechanisms (figure 4): (a) increase in glucose uptake by peripheral tissues (Pasteur effect), and (b) decrease in hepatic glucogenesis. With anoxia there is an increase in anaerobic glycolysis and in lactic acid, and a decrease in glycogen. Anoxia also inhibits gluconeogenesis, and leads to a decrease in liver glycogen and hepatic glucogenesis. Pyruvate, lactate and citrate accumulate in the blood. There is decreased lipogenesis and decreased oxidation by adipose tissue of glucose, acetate and succinate. Many compounds that inhibit oxidative phosphorylation increase glucose uptake and inhibit gluconeogenesis. Unlike other known compounds causing increased glucose uptake, insulin stimulates the same amount of uptake under aerobic as under anaerobic conditions; furthermore, insulin stimulates rather than

MECHANISM OF PHENETHYLBIGUANIDE HYPOGLYCEMIA

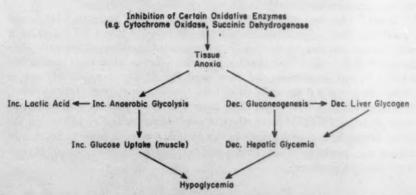


Fig. 4. As discussed in the text, there is evidence suggesting that PEBG inhibits oxidative phosphorylation; this could lead to anoxia. Conversely, anoxia can inhibit oxidative phosphorylation. There is insufficient information for concluding which is primary. However, in either instance the changes shown in the above figure could be expected, and have been demonstrated to occur under certain experimental conditions. (Modified after Williams, R. H., Steiner, D. F., Odell, W. D., Tanner, D. C., and Henley, E. D.: Oral therapy for diabetes, Proceedings of the Third Congress of the International Diabetes Federation, Dusseldorf, July, 1958, 1959, Georg Thieme, Stuttgart.)

inhibits oxidative phosphorylation. PEBG, by inhibiting oxidative phosphorylation, decreasing high energy phosphate and decreasing Krebs' cycle activity, could account for the lack of energy observed in some patients treated for months with this compound. Insulin rapidly reverses this clinical change, and can be expected to reverse some of the biochemical changes.

Studies in man have shed little light on the mechanism of action of PEBG. This is probably due at least partially to less detailed studies and to inability to detect some minor alterations.

Clinical Studies: In studying approximately 100 diabetics, we have found that PEBG causes a decrease in blood sugar by 30% or more in one-half of the subjects, with a 50% decrease in glycosuria, or a decrease in insulin requirements of 30% or more. There was no correlation of the response to therapy with age or duration of diabetes, but there was an inverse relationship to the previous dosage requirement for insulin.

Extensive use of the drug is hampered by two types of side-effect: ²⁴ (a) early, occurring usually within the first few days, and consisting of anorexia, nausea and vomiting, or (b) late, and consisting of lassitude, weakness and slight weight loss, observed one or more months after beginning therapy. The early side-effects have been observed by us in approximately one-half of the patients, and the late effects in about one third of those treated for from one to two months or longer. All side-effects disappeared within from one to three days after cessation of biguanide therapy. No permanent ill-effects have been reported. The smaller the dosage, the lower is the incidence of side-effects. In most patients it is preferable not to use more than 200 mg. daily. In some subjects, however, much larger amounts may be ingested without side-effects.

Krall ²⁵ observed side-effects in one third of 121 patients. He found "good" or "fair" control in 66 of 88 subjects. He found PEBG to be a very useful adjunct to insulin in a significant number of juvenile diabetics; ^{28, 28} indeed, it was possible to reduce the usual dose of insulin by 64%. In our experience, the chief need for PEBG is as an adjunct to insulin in juvenile diabetics. Also, used simultaneously with sulfonylureas, it is more effective than either drug alone. In some patients with maturity-onset diabetes, PEBG is more effective than insulin or sulfonylureas, but the latter are preferable oral agents in the majority of such patients because of their lower incidence of side-effects and because of the more normal physiologic changes produced.

SUMMARY AND CONCLUSIONS

Oral therapy for diabetes is a worthy objective, provided it appropriately controls the metabolic alterations of diabetes. The advantages must outweigh the disadvantages.

Three sulfonylureas have offered promise: tolbutamide, chlorpropamide

and metahexamide. They presumably lower the blood sugar by stimulating increased insulin secretion and by decreasing hepatic glucogenesis, particularly in the presence of insulin. They seem to have their greatest effect in patients who most nearly approach normality in the amount of assayable insulin in the plasma and pancreas; these tend to be elderly individuals with stable diabetes of recent onset. A poor response is apt to be obtained in depancreatized patients, or in diabetes that is unstable or of long duration, or requires large insulin doses, or is prone to produce keto-acidosis. There is no evidence that sulfonylurea treatment causes β cell exhaustion; indeed, there is more to suggest the contrary. Side-effects with tolbutamide have been few and mild. Chlorpropamide and metahexamide have caused side reactions more frequently, and occasionally have produced jaundice of the cholestatic type, usually reversed upon cessation of treatment. Metahexamide has caused jaundice with sufficient frequency to preclude its further use in this country.

Metahexamide and chlorpropamide are more potent than tolbutamide, but thus far this seems to have advantage in only a small proportion of

patients.

Phenethylbiguanide inhibits certain oxidative enzymes of the Krebs' cycle, particularly succinic dehydrogenase and cytochrome oxidase. This produces: (a) an increase in anaerobic glycolysis with an increase in glucose uptake, and (b) a decrease in gluconeogenesis, decreased liver glycogen and decreased hepatic glucogenesis. As a result, glucose disappearance from the blood increases and its entrance from the liver decreases, both factors contributing to hypoglycemia. This biguanide may lower the blood sugar in all types of diabetics, but the greatest effect is observed in the mild, stable type. Combined with insulin, it produces smoother control in unstable diabetics. In some subjects, chiefly of the stable type, better control is obtained with the biguanide plus a sulfonylurea than with either drug alone. The high incidence of side-effects, even though rapidly reversible, has significantly limited the extent of usage of phenethylbiguanide.

Tolbutamide, chlorpropamide and phenethylbiguanide all have value in the treatment of some diabetics. Moreover, many additional orally effective compounds will be provided. They must be evaluated objectively, noting their effects not only on the levels of glucose in the blood and urine but also upon many phases of the metabolism of carbohydrates, fats and proteins,

as well as their effect on general health with prolonged usage.

SUMMARIO IN INTERLINGUA

Le therapia oral de diabete es un objectivo de alte valor, providite que illo stabilisa appropriatemente le alterationes metabolic de diabete sin excessive disavantages. Tres sulfonylureas se ha provate promittente: Tolbutamido, chlorpropamido, e metahexamido. Presumitemente illos reduce le sucro del sanguine per stimular le secretion de insulina e reducer le glucogenese del hepate, particularmente in le

presentia de insulina. Il pare que illos exerce le plus grande effecto in patientes qui attinge le plus grande approximation al stato normal con respecto al quantitate essayabile de insulina in le plasma e in le pancreas. Iste patientes es frequentemente subjectos de etate avantiate con diabete de declaration recente. Un responsa pauco favorabile pote esser expectate in patientes pancreatectomisate e in casos de diabete que es instabile, que es de longe duration, que require grande doses de insulina, o que se distingue per le tendentia de disveloppar ceto-acidosis. Il existe nulle prova que le therapia a sulfonylurea exhauri le cellulas beta; de facto, il ha datos que suggere le contrario. Le effectos lateral causate per tolbutamido ha essite leve e pauco numerose. Chlorpropamido a metahexamido ha causate plus frequente reactiones lateral. In casos sporadic illos ha causate ictero del typo cholestatic, sed isto se reverteva usualmente post le discontinuation del therapia. În le caso de metahexamido le causation de ictero ha essite satis frequente pro terminar le uso de iste droga in le Statos Unite. Metahexamido e chlorpropamido es plus potente que tolbutamido, sed usque nunc il pare que iste facto beneficia solmente un micre numero de patientes. Phenethylbiguanido inhibi certe enzymas de oxydation in le cyclo de Krebs, particularmente dishydrogenase succinic e oxydase cytochrome. Isto produce (a) un augmento de glycolyse anaerobie con le augmento del acceptation de glucosa e (b) un reduction del gluconeogenese, del glycogeno hepatic e del glucogenese hepatic. Per consequente, glucosa dispare plus rapidemente ab le sanguine durante que su entrata ab le hepate es relentate, e ambe iste factores contribue al disveloppamento de hypoglycemia. Iste biguanido pote reducer le sucro del sanguine in omne le typos de diabeticos, sed su plus pronunciate effecto es observate in casos del typo leve e stabile. Combinate con insulina, illo resulta in un plus lisie regulation de diabete in patientes instabile. In certe subjectos, principalmente del typo stabile, un melior regulation es obtenite per biguanido in combination con un sulfonylurea que per le un o le altere del duo drogas sol. Le alte incidentia de effectos lateral-ben que istos es rapidemente reversibleha significativemente reducite le mesura del utilisation de phenethylbiguanido.

Tolbutamido, chlorpropamido, e phenethylbiguanido es omnes de valor in le tractamento del un o del altere gruppo de diabeticos. In le futuro, multe nove e efficace oral agentes antidiabetic va esser trovate. Illos debe esser evalutate objectivemente. Un tal evalutation se concerne non solmente de lor effecto super le nivello de glucosa in le sanguine e le urina sed etiam de varie phases del metabolismo de hydratos de carbon, de grassia, e de proteina e de lor effecto general super le sanitate del patiente tractate con illos a longe durantia.

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EXPERIMENTAL LAENNEC TYPE OF CIRRHOSIS IN MONKEYS*

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DESPITE extensive research, no proved concept of the etiology of Laennec's cirrhosis has yet been established. Cirrhosis has been produced experimentally by different means in several species (mice, rats, guinea pigs, rabbits, dogs).1-21 However, some pathologists have contended that the resulting lesions lack certain criteria that permit the diagnosis of Laennec's cirrhosis and would not allow any application to man. It was therefore felt that an experimental reproduction of Laennec's cirrhosis in primates might shed some light on this complex problem in man. Little work has been done so far on primates. After numerous failures using various abnormal diets on several Cebus and Rhesus monkeys, we wish to report the successful production, by dietary means, of a Laennec type of cirrhosis in two out of two male Cebus monkeys. This experiment will serve as the basis for a discussion of the etiology of cirrhosis in man.

METHODS AND MATERIALS

The two male animals employed in this study arrived in the colony in Toronto four years ago (1955), and were given a well balanced natural diet for six months. They were around two or three years of age. The monkeys gained weight and acclimated well to their new environment. Thereafter, these two animals were fed a "complete" purified diet, and served as cholinesupplemented controls in a study that lasted about one year.²² During this time two large pieces of liver (7 to 9 gm. of fresh tissue) were removed surgically by laparotomies which were performed half a year apart. On both occasions the livers of these two animals were found to be free of any stainable fat, showed no signs of parasitic infestation, and appeared to be normal in every respect.

At a weight of 2.2 and 2.5 Kg., respectively, the monkeys were transferred to a cirrhogenic diet (MK-4, table 1) which is low in protein, free of appreciable amounts of choline, and rich in cholesterol. After being on this cirrhogenic regimen for four months they were transferred to the cirrhogenic diet MK-6, which has even less protein (table 1). Five months later the

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TABLE 1

Composition of Cirrhogenic Diets MK-4 and MK-6 (The diets were offered in the form of biscuits)*

| | MK-4 | MIK-6 |
|------------------------------------|------|-------|
| Alpha soya protein† | 10 | - 5 |
| Alcohol-extracted peanutmealt | 10 | 10 |
| Salt mixtures | 3 | 3 |
| Sucrose | 33 | 52 |
| Starch | 13 | 5 |
| Dextrine | 13 | 5 |
| Lard | 16 | 18 |
| Cholesterol | 2 | 2 |
| Vitamine were added after baking * | | |

* For the details of the preparation of biscuits by a baking technic see J. Exper. Med. 108: 361, 1958.

Obtained from Archer-Daniels-Midland Company, Cincinnati, Ohio.

Extracted with 50, 75 and 90% hot ethanol.

For details see Canad. J. M. Sc. 3: 135, 1953.

The vitamin mixture used contained all vitamins (including small amounts of B₁₂) with the exception of choline. For details see J. Exper. Med. 108: 361, 1958.

condition of the animals had deteriorated, and consequently they were given a complete diet (MKA) for about six weeks. Then they were fed the cirrhogenic diet (MK-6) for another six months. During this period they were given small amounts of fresh cabbage in an attempt to stimulate their consumption of the deficient cirrhogenic diet MK-6. Again their condition deteriorated, and they were transferred to the nutritious diet (MKA) for 10 days, after which the first experimental laparotomy was performed. The animals recuperated slowly after the first experimental laparotomy. They were given the fully nutritious, protein-rich diet MKA for another nine months after laparotomy. Eventually their health improved markedly, and a considerable weight gain was observed. This administration of an adequate diet was carried out to evaluate whether the cirrhotic process could be brought to a halt or perhaps could even be reversed. On the other hand, the possibility had to be considered that the cirrhosis in our monkeys

TABLE 2

Composition of the Nutritious, Fully Adequate Diet MKA (This diet was offered in the form of biscuits which were freshly prepared twice weekly)

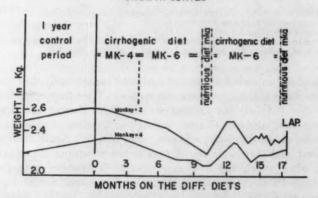
| Dried egg yolk, "Borden" Whole milk powder, "Borden" | | 800 gm. 400 gm. |
|--|---|--------------------|
| Whole wheat flour Sucrose | | 980 gm. 700 gm. |
| Salt mixture* Baking powder | J | 120 gm. |
| Water | | 15,00 ml. |
| Mix and bake at 350° Fahrenheit for 30 minutes. Vitamins† were added after baking. | | |

* For details see Canad. J. M. Sc. 3: 135, 1953.
† The vitamin mixture used contained all vitamins (including small amounts of B₁₉) with the exception of choline. The latter, however, is abundantly supplied in egg yolk. For details see J. Exper. Med. 108: 361, 1958.

would perpetuate itself despite the therapeutic consumption of an adequate diet after having passed a point of reversibility. After these nine months of therapeutic administration of an adequate diet, a second experimental laparotomy was performed. The animals are still alive and will continue to serve in a long-term study.

The composition of diets MK-4, MK-6 and MKA can be seen in tables 1 and 2. The sequence of the feeding schedules up to the first experimental laparotomy is outlined in text figure 1. A condensed summary of the experimental course is given below.

GROWTH CURVES



6 months 12 months 17 months

9 months

44 months total

Adjustment to our colony after purchase.
Control period with two control biopsies.
Induction of cirrhosis. First experimental laparotomy.

Therapeutic administration of adequate diet. Second experimental laparotomy.

The housing care of the animals and the preparation of the diets have previously been described.²²

At both experimental laparotomies (August 20, 1958, and April 7, 1959), performed under Nembutal anesthesia (continued with ether as necessary), 7 to 10 gm. of liver were taken by surgical resection for histologic examination and liver lipid determinations. The histologic material was fixed in 10% formalin for frozen sections, and in Helly's fixative for paraffin sections. Frozen sections were stained with 0.4% Oil Red O in triethylphosphate. Hematoxylin-eosin and Masson's trichrome stains were done on paraffin sections. Blood was withdrawn for serum protein determinations (table 4) and blood smears. The references for the biochemical determinations of liver lipids and serum proteins are given in tables 3 and 4.

TABLE 3 Biochemical Data on Monkey Liver Biopsies No. 2 and No. 4 (a) Liver lipids*

| Liver dffr.† %w. wt.‡ | | Total Lipids | | Phospho- lipids | | Cholesterol | | | | | Oleate | | Glyceride | | |
|--------------------------------|----------------|----------------|---------------|--------------------|----------------|--------------|---------------|-------------|-------|--------------|---------------|--------------|---------------|---------------|--------|
| | Total Lipids | | lipids | | To | tal | I Free | | Bound | | Office | | Glyceride | | |
| | wt.‡ | %w. wt.‡ | dir.t | %w. wt.‡ | der.t | %w. wt.‡ | dir.† | %w. wt.‡ | dfr.† | %w. wt.‡ | dar.t | %w. wt.‡ | dfr.† | %w. wt.‡ | dffr.1 |
| No. 2 No. 4 | 11.06 13.55 | 13.33 24.95 | 83.3 184.1 | 2.11 2.02 | 13.69 14.87 | 0.85 5.28 | 5.62 38.94 | 0.40 | 1.97 | 0.56 4.74 | 3.65 34.94 | 0.94 7.96 | 6.13 58.70 | 9.98 14.43 | 62.0 |

(b) Connective tissue

| Nitrogen§ mg./100 mg. dffr.* | Hydroxyproline mg./gm. of dffr. | Collagen¶ % of dffr.* |
|---------------------------------|---------------------------------|--------------------------|
| 12.7 | 9.5 | 7.1 |

* For details of the methods used see J. Exper. Med. 108: 361, 1958.
† dffr. = dry fat-free residue.
‡ w.wt. = wet weight.

Micro-Kjeldahl: Ma, T. S., and Zuazuga, G.: Ind. Eng. Chem., Anal. Ed. 14: 280, 1942.
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Collagen is computed by converting hydroxyproline mg_/gm. to collagen by the use of the factor 7.46.

TERMINOLOGY

Although it has been suggested that the term Laennec's cirrhosis be abandoned in favor of portal cirrhosis,28 we felt that we should adhere to the older term. While the controlled conditions of our experiment permit a consideration of the etiology of the cirrhosis produced in our monkeys, it is

TABLE 4 Serum Protein Data, gm.% (Paper electrophoresis*)

| MK-2 | Control | 1st Exper. Laparotomy | 2nd Exper. Laparotomy |
|---|----------------------|--------------------------|--------------------------|
| Total protein Albumin Alpha Beta globulin Gamma A/G ratio | 8.21 | 9.6 | 9.81 |
| | 5.26 | 4.08 | 4.56 |
| | 0.81 | 0.99 | 1.60 |
| | 0.90 | 0.86 | 1.10 |
| | 1.25 | 3.68 | 2.54 |
| | 1.8 | 0.73 | 0.86 |
| MK-4 | (on the later of the | | 14, 22 |
| Total protein Albumin Alpha Beta globulin Gamma A/G ratio | 7.55 | 9.97 | 8.92 |
| | 4.94 | 5.23 | 4.01 |
| | 0.77 | 0.76 | 1.91 |
| | 0.77 | 0.99 | 0.91 |
| | 1.06 | 3.00 | 2.10 |
| | 1.93 | 1.1 | 0.81 |

^{*} Kunkel, H. G.: Simple paper electrophoresis. Methods of biochemical analysis, Vol. I, edited by D. Glick, 1954, Interscience Publishing Company, New York, p. 144.

obvious that the elucidation of the *pathogenesis* awaits more extensive study. The term Laennec's cirrhosis describes the morphologic end-result of a variety of liver injuries. It is noncommittal as to how the initial stages of the condition develop into their final picture. Since we are not certain about the pathogenesis of the cirrhosis in our monkeys, we felt that the continued use of the noncommittal term Laennec's cirrhosis was advisable under these particular circumstances.

RESULTS

I. Weight and Growth: When the two monkeys were fed diets MK-4 and MK-6 (mostly the latter) to induce cirrhosis, a gradual loss of weight occurred (text figure 1). The food intake on diets MK-4 and MK-6 was only moderate compared to that during the previous control period on the choline-supplemented diet, and it was subject to great variations. After somewhat more than nine months on this regimen, the condition of the animals had become precarious. They were emaciated and irritable, had begun to lose hair, and had developed small skin ulcers, located mostly on the tail. When given the nutritious diet MKA they recuperated slowly and eventually ate rather large quantities of this complete diet. When there was a reasonable degree of rehabilitation they were offered the cirrhogenic diet MK-6; they soon started to lose weight again. After the weight had reached its lowest point it began to rise slowly and showed great fluctuations, due to varying degrees of water retention and ascites (very definite in monkey No. 2, less conspicuous in monkey No. 4). These fluctuations are obvious in text figure 1.

After the first laparotomy the animals were continued on the adequate, protein-rich diet MKA for another nine months, and consequently their appetite increased. They began to gain a considerable amount of weight. The weight gain was a true one, since the adequate diet enabled the animals to rid themselves of the excessive amounts of water retained in the tissues and the peritoneal cavity. In this therapeutic period of consumption of an adequate diet, the general health of the animals reverted to normal: the skin ulcers healed, their fur became smooth again, and their restlessness subsided. Undue scratching was no longer noticeable. However, as will be discussed below, despite this remarkable clinical rehabilitation the histologic picture of the livers, although remarkably improved, did not come back to normal again. The weight of the two animals at the second laparotomy was 2.9 Kg. for monkey No. 2 and 2.6 Kg. for monkey No. 4.

II. Findings upon the First Experimental Laparotomy:

(a) Clinical. On the day of the first experimental laparotomy the animals looked wasted and drawn, despite the improved nutrition during the preceding 10-day period. They were, however, still very active, and leaped around trying to escape being caught. Both monkeys were distinctly icteric and scratched constantly (more pronounced in animal No. 2 than in No. 4).

The abdomen of monkey No. 2 was slightly protruding. Venous collaterals were distinctly visible on the abdominal wall, reaching upwards to the chest (figure 1). The animal had lost a considerable amount of its fur, and many medium sized, shallow skin ulcers were visible, predominantly on the tail and over areas of pressure or friction. About 40 c.c. of ascitic fluid were found in the peritoneal cavity. The liver, which was palpable under anesthesia, was enlarged, tawny yellowish and firm, with several large nodules scattered over a very finely granulated surface. There was no sign of biliary stasis in the common bile duct. The gall-bladder emptied promptly upon manual pressure. The spleen was enlarged and rather firm, with fibrous thickening of the sugar-coating type. No other observations within the abdomen were possible, as the incision had been kept reasonably small.



Fig. 1. Monkey No. 2 prior to laparotomy. Note the loss of fur and the distinctly visible, dilated vein extending from the upper abdomen to the wall of the chest.

Monkey No. 4 had some loss of hair and two small skin ulcers among numerous scratch-marks. The liver could be felt even without anesthesia, but upon laparotomy no ascites was present. The liver was larger and yellower than that of animal No. 2. It was also more coarsely granular, and its consistency was firmer (figures 2 and 3). The superficial nodules were smaller than in the other animal but more numerous. Again no sign of biliary stasis was detectable. The spleen was enlarged and of normal consistency, and its surface was smooth and shiny.

The animals withstood both the laparotomy and the removal of about 10 gm. of fresh liver tissue reasonably well. They were kept on the nutritious diet MKA after the laparotomy, and continued to recuperate and to gain strength.



Fig. 2. Monkey No. 4 at laparotomy. The liver is exposed and shows signs of granularity.

(b) Biochemical Findings on the First Experimental Biopsy Specimens: In liver No. 4 a rather large amount of extractable lipid was present (table 3). The very high cholesterol content of the liver is noteworthy. Most of this cholesterol is in the bound form.



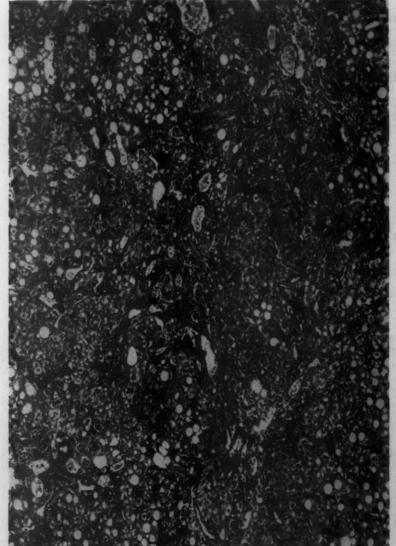
Fig. 3. The cirrhotic liver of monkey No. 4 at a close-up. The liver is enlarged. The surface of the liver is finely granular and studded with visibly protruding nodules.

The hydroxyproline content of the dry, defatted liver tissue was increased considerably above the normal values observed in our strain of rats; we have no data on normal monkey liver tissue as yet. The hydroxyproline found in the livers of 10 normal rats was 0.79 to 1.14 mg. per gram dry, fat-free residue, with a mean value of $0.97 \pm \text{s.d.} 0.12$. The biopsy specimens from the monkey livers contained 10 times this proportion of hydroxyproline, corresponding to about 7.2% collagen. These chemical data confirm the histologic evidence that there is pronounced increase in the connective tissue.

No liver function tests were done in this study because of the animals' precarious condition. It was felt that no risk should be taken that would be out of proportion to the information likely to be obtained by the pro-

cedures.

- (c) Serum Proteins: The serum proteins showed distinct changes as compared with the control period (table 4). The comparatively high amount of total protein present at laparotomy was probably due in part to dehydration of the animals during the surgical procedure. It therefore seems more appropriate to compare the ratios of the individual fractions than to draw any conclusion from the absolute amount of protein present in each fraction. On this basis it can be seen that there is a slight decrease in the serum albumin fraction, while there are distinct increases in all globulin fractions, particularly in the alpha and the gamma globulin. The alpha and gamma globulins have risen by about 100% as compared with the values in the control period. Consequently, the albumin/globulin ratio, which had a value of roughly 1.8 in the control period, fell to a value of 0.85. This reversal of the A/G ratio has been observed in many cases of human cirrhosis, and also in other forms of disease in which either protein metabolic or immunologic factors are claimed to have a significant causality. The reversal of the A/G ratio in our cirrhotic monkeys is in keeping with these clinical observations.
- (d) Histologic Examination: Most features of Laennec's cirrhosis were present in both livers. Biopsy specimen No. 2 revealed a moderately fatty liver with signs of active (florid) cirrhosis (figures 4 and 5). Inflammatory and fibroblastic activity was seen everywhere, but was definitely predominant in the periportal areas, with large numbers of fibroblasts, leukocytes, plasma cells and lymphocytes disguising the normal liver architecture. There was big and small droplet lipid accumulation everywhere. Some fatty cysts, as described by Hartroft ¹⁰ could be discovered in this specimen. Liver cell degeneration and necrosis were conspicuous. Liver specimen No. 4 illustrated a more advanced state of portal cirrhosis (figures 6–9). Large quantities of young, slightly edematous, only moderately cellrich connective tissue were distributed diffusely throughout the section, but were located in slightly increased degrees in the periportal areas. Whether connective tissue formation started pericentrally or periportally cannot be decided on the basis of these two specimens, as the lesions were



Fro. 4. Medium power, Masson trichrome stain. Monkey No. 2: florid (active) cirrhosis. The normal liver architecture is completely distorted. Most liver cells show signs of degeneration. There are some fatty cysts, the localization of which cannot be determined with accuracy. The most striking feature is the high degree of inflammatory activity. Large numbers of inflammatory cells are crowded around two periportal areas and connect with each other. The preexisting normal lobular pattern of the liver cell cords is divided by this inflitate into several compartments of irregular size and contour. Some diffusely distributed connective tissue is demonstrable.

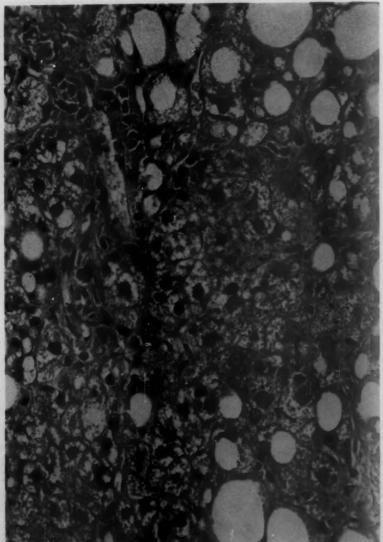


Fig. 5. High power, H and E stain. Monkey No. 2: florid (active) cirrhosis. A terminal branch of the portal vein is visible in the right upper corner of this high power photograph. In its immediate vicinity, large numbers of leukocytes, prophocytes, plasma cells and fibroblasts are illustrated. Even eosinophils may be found in this infittate. The liver cells show signs of fat accumulation and degeneration. Their cytoplasm is foamy and lacks its normal density. In the left lower corner two Mallory bodies (alcoholic hyalin) are indicated by an arrow. Connective tissue strands are detectable by histochemical tests, but are not so conspicuous in this specimen of active (florid) cirrhosis as in monkey No. 4.



They contain less fat than their neighboring degenerated liver cells. Also, they are "encapsulated" by fine strands of young connective tissue bands completely disorganize the normal liver architecture. There seems to be a slight increase of connective tissue elements in the portal areas as compared with nonportal regions. Large numbers of fatty cysts are distributed throughout this specimen. Here, too, an accurate localization of the fatty cysts is impossible, as the cirrhotic process has advanced too far. Fig. 6. Low power, Masson trichrome stain. Early Laennec's cirrhosis in monkey No. 4. Large amounts of young connective tissue bands are scattered throughout the entire section. Frequently these bands "connect" portal triad with portal triad, or with a central vein. There are numerous regenerating nodules which are easily recognized. They contain less fat than their neighboring degenerated liver cells. Also, they are "encapsulated" by fine strands

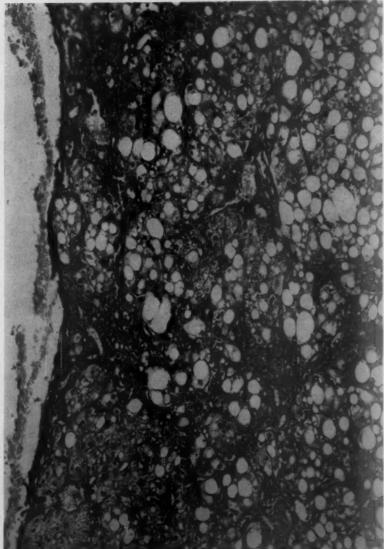


Fig. 7. Medium power, Masson trichrome stain. Early Laennec's cirrhosis in monkey No. 4. This photograph accounts for the granular and nodular appearance of the surface of this cirrhotic liver. Diffusely spreading connective tissue bands "pull" the capsule of the liver inward (right side of the picture), while a regenerating nodule protrudes outward (left side of the picture). In this area, too, it cannot be stated with creatinty whether fat is predominantly in a periportal or a pericentral location. The periportal areas show increased connective tissue formation and cellular inflitration. Connective tissue bands are, however, visible in nonportal areas as well.

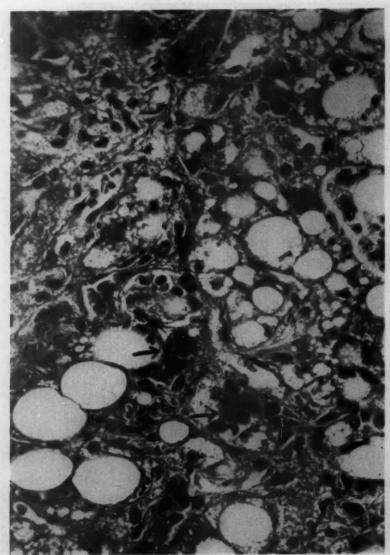
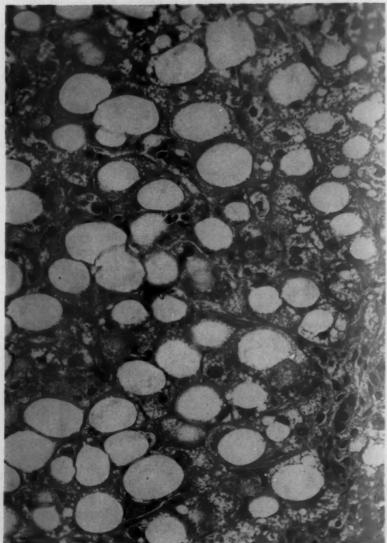


Fig. 8. High power, Masson trichrome stain. Early cirrhosis in monkey No. 4. The extensive degrees of fat accumulation and cellular degeneration are demonstrated in a region where connective tissue formation is conspicuous. Fine collagenous strands are intermingled with fibroblasts and lymphocytes. Polymorphonuclear leukocytes are scanty. The arrows indicate alcoholic hyalin (Mallory's bodies).



Fro. 9. High power, H and E stain. Early cirrhosis in monkey No. 4. Great numbers of large, confluent fatty express appear in all parts of this picture. Note how fine connective tissue strands "embrace" groups of fatty cells, separating them from each other. The cytoplasm of the liver cells is thinned to a narrow rim, and the nucleus is displaced into a corner. The remnants of the cytoplasm are foamy and reticulated. A group of fibroblasts is to be seen in the left lower part of the photograph, and a few inflammatory cells appear at random.

too far advanced at the time of biopsy. Regenerative liver cell nodules were frequently seen, and were "encapsulated" by fine strands of connective tissue. The hepatic cells in these areas of regeneration had accumulated less fat than had the surrounding degenerating cells. These nodules and connective tissue bands separated the liver cell cords, which no longer exhibited their normal arrangement. Confluent fatty cysts were frequently observed in this liver, but no decision could be made with certainty as to whether the lipid accumulation was predominantly periportal or pericentral, because the pathologic changes were too advanced, and the normal liver architecture was no longer recognizable. Upon examination of frozen sections with Nicol prisms we could observe cholesterol crystals either within surviving liver cells or lying freely between parenchyma and connective tissue. Numerous Mallory bodies 24 were detectable in both specimens by the Masson trichrome technic and also by hematoxylin-eosin stains. Blood smears illustrated a normochromic anemia.

III. Findings at the Second Experimental Laparotomy:

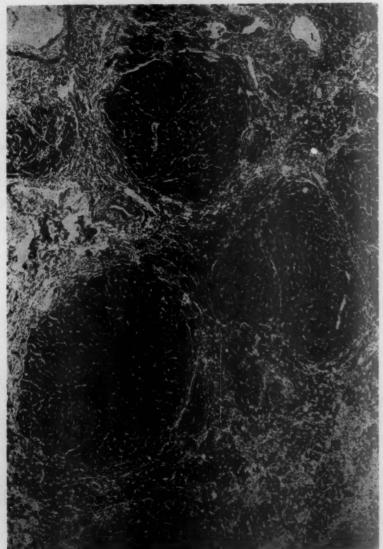
(a) Clinical: The signs of portal hypertension, so easily detectable at the first laparotomy, had vanished in the course of the therapeutic administration of the protein-rich, nutritious diet. There was no more venous collateral distention or ascites, and the icterus had disappeared.

Surgery was becoming difficult at the second laparotomy, due to numerous adhesions from the three earlier surgical procedures. Both livers were practically normal in size and had again acquired their normal reddish brown color. The surface of both livers was smooth, although upon inspection with a magnifying lens a very fine granulation was still detectable. The coarse granulation and nodular appearance of the fatty livers at the first experimental laparotomy had all but completely disappeared. However, grayish connective tissue bands were visible, and a nodular pattern distorted the normal architectural appearance on the cut liver surface.

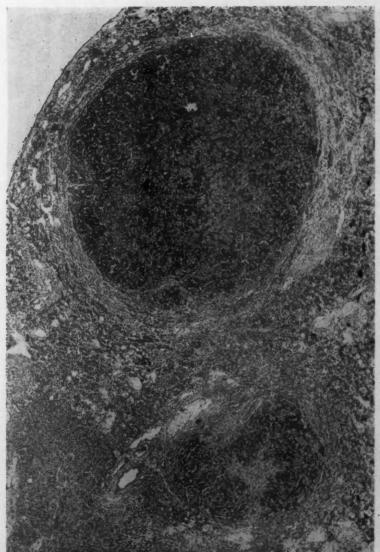
The spleens were still enlarged and had a thickened capsule and several fibrotic nodules. Again, no signs of biliary obstruction were detectable.

(b) Biochemical Findings. In both animals the liver total lipids amounted to 14% of the liver wet weight. The normal values obtained in the control period were between 6 and 8%. Thus the total lipid content was still somewhat elevated, but was considerably less than the 24% recorded in monkey No. 4 at the first experimental laparotomy. This decrease of liver lipids was also borne out by clinical inspection at surgery and by histologic examination.

(c) Serum Proteins. The serum protein determinations done at the time of the second experimental laparotomy are essentially the same as the ones obtained at the first experimental surgery (table 4). Despite the consumption of an adequate, protein-rich diet, the A/G ratio did not come back to normal, but stayed at its former inversed level. This may be taken as a



Fro. 10. Histology of cirrhotic livers after consumption of a therapeutic protein-rich diet. Nodular regeneration is the most conspicuous feature in this low power photomicrograph. Several large nodules of regeneration are encapsulated by connective issue bands, which seem to have been condensed during the process of architectural reconstruction. There is bile duct proliferation which is, however, better demonstrable under higher power. Several areas show resorption of liver cells by an invading granulation tissue. McGregor's connective tissue stain.



Fro. 11. The same processes of architectural reconstruction as shown in figure 10 are demonstrated in this frozen section, which has been stained for fat with Oil Red O. Stainable lipid appears only in small amounts after the administration of a protein-rich therapeutic diet. Although therapy brought about a marked clinical improvement of the animals, the livers still show distinctly a continuation of the processes of repair, which are responsible for the production of cirrhosis.

sign that, despite good clinical rehabilitation and signs of histologic liver cell regeneration, some processes of protein metabolism continue to show

profound changes.

(d) Histology of the Second Experimental Biopsies: The most striking histologic feature in both biopsy specimens obtained at the second experimental laparotomy was a pronounced degree of nodular regeneration (figures 10 and 11). In both livers, signs of very active architectural reconstruction were unmistakably present. Numerous large regeneration nodules composed of healthy looking liver cells dominated the picture. There was also a rather striking degree of bile duct proliferation. The connective tissue bands, distributed previously in a diffuse manner throughout the section. were now confined to condensed strands being "pushed" aside by the regeneration nodules. In some areas, resorption of remaining parenchyma was noticeable, leaving dying and partly disintegrated liver cells behind, which were phagocytized by a cell-rich granulation tissue. Occasionally, fine connective tissue strands were found in these areas of resorption. Whether they are remains of formerly present collagen or whether they are newly laid down is hard to decide on the basis of a histologic section. A great portion of the fat, so striking at the first laparotomy, had disappeared from both healthy and degenerating liver cells, thus accounting for the normal color and the reduced size of the liver in the gross. A decrease in intrahepatic tissue pressure may account in part for the disappearance of ascites and icterus at this stage of the pathologic process. It is impossible, in a study like this one, to come to any definite conclusion as to whether collagen is resorbable. The appearance of the connective tissue had certainly changed. It had become compressed into certain areas, but a dynamic process like collagen formation cannot be followed by random histologic sampling. Summarizing, we would like to point out that both livers, although removed from any form of external injury, still continued to show striking signs of regeneration, resorption and architectural reconstruction. The final outcome of this process-whether approaching normality or progressing towards functional insufficiency caused by complete architectural distortion—has to be elaborated by future studies.

DISCUSSION AND CLINICAL INTERPRETATION

The discussion may be conveniently arranged under three main headings:

- (a) Experimental findings.
- (b) Etiology.
- (c) Therapy.
- (a) Experimental findings: Early cirrhosis of the Laennec type was produced in two Cebus monkeys by a dietary regimen that consisted of feeding of diets low in protein, free of appreciable amounts of choline, and rich

in cholesterol (2%), intermittently followed by a well balanced, nutritious food that was offered to the animals on two occasions to prevent their death. The transfer from cirrhogenic diet MK-4 to the more severe diet MK-6 was undertaken to speed up the process of cirrhogenesis after an initial period of dietary adjustment.

The cirrhosis observed could not have been preëxisting or due to a preceding florid infectious or parasitic process, otherwise signs of these pathologic conditions would have been detected in the two control biopsies. The cirrhosis in these two animals seems obviously to have been brought about by dietary manipulations.

The hepatic changes produced fulfilled most if not all classic criteria that permit the diagnosis of "Laennec's cirrhosis" (table 5). We observed diffuse fibrous bands with a slight increase of connective tissue in the portal

TABLE 5

Summary of the Findings in the Two Cirrhotic Monkeys as They Relate to Human Laennec's Cirrhosis

I. Clinical:

- a) Liver: Tawny yellow color, increased firmness, granular surface studded with nodules.
- b) Portal hypertension, hypersplenism, ascites, venous collaterals.

II. Histologic:

- a) Degeneration and necrosis of hepatic cells, Mallory bodies.
 b) Diffusely distributed fibrous bands with increased connective tissue around portal triads. The fibrous bands "connect" either with other portal regions or with central areas.
- c) Nodular regeneration.

III. Biochemical:

- a) Increased liver lipid content.
- b) Increased amounts of hepatic connective tissue.
- c) Serum albumin decreased, serum globulins increased. Inversion of the A/G ratio.

There were hepatic cell degeneration and necrosis, as proved by the presence of numerous Mallory bodies. Nodular regeneration was distinct. In one animal, signs of inflammatory infiltrates, located most conspicuously in the portal triads, gave evidence of an active (florid) cirrhosis. There were clinical signs of portal hypertension, hypersplenism, ascites and icterus.

A complete interpretation of the pathogenesis of the cirrhosis produced in our two animals awaits further study and will not be attempted here. The etiology of these hepatic changes, however, may be subjected to a critical, albeit preliminary, analysis. For obvious reasons, one cannot make any direct clinical applications to cirrhosis as observed in man from the findings in our monkeys. Despite the close species relationship between man and monkeys, one must not forget that the experimental regimen to which our monkeys were exposed has no direct clinical counterpart. However, our study may be taken as an experimental model. Critical analysis of the

situation may provide insight into some of the processes that may be responsible for the induction of cirrhosis in man.

(b) Etiology: Several etiologic factors, direct and indirect, may in our monkeys play a role in the induction of the liver changes that closely resemble Laennec's cirrhosis as observed in man. A diet low in protein and free of choline (like diet MK-6) might conceivably activate latent infections. The inflammatory periportal infiltrate in monkey No. 2 would be in keeping with this assumption. However, the two control liver biopsies done prior to the beginning of the experiment showed that chronic infections were undetectable in the liver; if any infection was present, it did not harm the animals when they were being fed an adequate diet. Another factor is dietary cholesterol, which is retained in larger amounts in the liver than would be the case if it were incorporated in a well balanced diet. The same amount of cholesterol seems to be nontoxic when given in a complete diet to monkeys.25 However, its retention in the liver when incorporated into a low protein, choline-free diet may lead to "irritation" that provokes hepatic cell damage, with regeneration and connective tissue proliferation as an ensuing response to this injury. Previous experience in our laboratory has shown the factors mentioned to be ineffective in the production of cirrhosis when monkeys are fed a well balanced diet.26 Therefore, the low protein content of diet MK-6 and absence of choline are probably important etiologic factors in our experiment. Another possible causative factor, cyclic feeding (alternation of deficient and complete diets), may enable the animal to survive long enough to eat more of the poor diet. One may assume that connective tissue formation and nodular regeneration require adequate dietary protein, and therefore would not proceed to a great extent on rations low in protein. These episodes of consumption of adequate food are therefore conceivably responsible for the occurrence of regenerating nodules and of connective tissue proliferation leading to the picture of cirrhosis. Whether accumulation in the liver of lipids other than cholesterol might play a role in the induction of this type of cirrhosis remains to be determined. On the basis of previous experience, we feel reasonably sure that the vitamin and mineral content of the diet was adequate and has no bearing on the development of the cirrhosis under our experimental conditions.

Further studies will have to establish if and to what degree poor diet, cholesterol and cyclic feeding, as separate factors, are essential for the induction of experimental cirrhosis of the Laennec type produced in our monkeys. However, this combination of stresses imitates what many authors ²⁷⁻³⁰ believe to be necessary for the occurrence of cirrhosis in man, namely, an increased vulnerability of the hepatic cells, which are further subjected to one of many possible types of liver injury occurring in successive episodes. An increased vulnerability of the liver cells may be the consequence of nutritional inadequacies, as was the case in our experiment. One

is forced to assume that an increased vulnerability of liver cells may also be inherent in some clinical cases, as cirrhosis may develop in patients where dietary inadequacies can be (or seem to be) ruled out. The reasons for this inherent vulnerability are unknown to us.

It is speculated, however, that in some cases where malnutrition can be ruled out, processes of "auto-immunization" may lead to continued liver cell damage and also to cirrhosis. 31-86 This theory is attractive, and could account for some cases of "idiopathic" cirrhosis. It could also explain why many cases of cirrhosis progress toward a fatal outcome despite removal of the patient from exposure to liver injury and despite good therapeutic management. In other words, it would help to explain why some cases of cirrhosis go into an irreversible phase. However, the proof of this attractive theory rests with the investigator. At the time of writing, no conclusive evidence has been provided that circulating auto-antibodies against liver can be demonstrated in cirrhotic patients, although complement-fixing antibodies could be shown to occur in some special cases of hepatitis (socalled lupoid hepatitis 35). It remains to be established whether antibodyantigen reactions in the classic sense are involved in the self-perpetuation of cirrhosis. But one may speculate that "some aberrations" of protein metabolism contribute to the continuation of cirrhosis. These aberrations are associated with increases in the globulin fractions of the serum proteins. Our serum protein data show decreases in albumin and increases in the globulin fractions, particularly in the alpha and gamma globulins, with the result that the A/G ratio becomes inversed. Because this inversion of the A/G ratio occurs in a variety of conditions, it is not specific for cirrhosis and admittedly does not prove the concept of auto-immunization. It is felt, however, that our serum data may serve as a guide for future inquiry concerning the possible validity of these newer concepts.

(c) Therapy: The therapeutic measures applied to our cirrhotic monkeys were effective in improving the clinical condition of our animals but did not revert the histologic picture and the A/G ratio to normal. It was to be expected that some connective tissue in these cirrhotic livers would remain despite rehabilitation of the animal. The fundamental question as to whether connective tissue stays "fixed" or may be resorbed to some extent under proper management cannot be decided here. However, stainable lipid in the livers of our animals had all but disappeared, and large regeneration nodules were unmistakably present. The final outcome of these reparative processes is under investigation. Since both animals are still alive, they will doubtless continue to provide data that will answer some of the questions which remain unsolved at present.

Conclusions

Although our study extended over a period of four years, it is still to be considered a pilot experiment. Therefore, it is too early to come to any definite conclusions as to the etiology of human Laennec's cirrhosis on the

basis of the work reported here. However, our data—clinical, histologic and biochemical—are in keeping with the clinicopathologic concept that the occurrence of cirrhosis depends not upon a single etiological factor but on a combination of causes. Cirrhosis develops as a phenomenon of repair in a liver which is susceptible to injury. The injury may occur either in successive episodes, or mildly, in a continued fashion.

The repair of injured parenchyma in other organs, like lung, heart and kidney, leads to scar formation or to hypertrophy of remaining parts, but not to regeneration of new architectural units. It is peculiar to the liver to repair damage by regeneration of parenchymatous cells. If regeneration is extensive, it is followed by architectural disorganization which, together with connective tissue formation, leads to the picture of cirrhosis. Liver injury and processes of repair in the liver are therefore equally important in the *production* of cirrhosis. The *perpetuation* of cirrhosis after its induction may be associated with changes in the serum protein patterns. This may imply that immunization of the body against its own liver cell protein—altered by injury—is another etiologic factor to be considered. Thus, the mechanism of perpetuation of cirrhosis may be different from the mechanism of its initial induction. This inference, if proved to be correct, might change our thinking and understanding of cirrhosis.

We cannot propose a theory that will fully explain the etiology of cirrhosis. But we believe that our study lends experimental support to the recent clinical concepts mentioned above, and might help to give new perspectives to the theory and treatment of cirrhosis.

·SUMMARY

(a) Experimental: Two male Cebus monkeys (three to five years of age) served as their own controls for a preliminary observation period of one and a half years, after which time they were given a cirrhogenic diet for 17 months. For two brief intervals during these 17 months they received a complete, nutritious diet to prevent their death. The cirrhogenic diet was low in protein, free of choline and rich in cholesterol (2%). Both animals developed a Laennec type of early cirrhosis. So far, other methods have failed to produce cirrhosis in monkeys.

(b) Therapeutic: After the diagnosis was established by laparotomy and histopathology, the animals were given a fully nutritious regimen as a therapeutic trial for nine months. Portal hypertension, ascites and icterus disappeared. The clinical condition of the animals and the gross appearance of their livers improved considerably, but the histologic picture could not be restored to normal within that period. Serum protein determinations showed an inversion of the A/G ratio, which persisted despite proper therapeutic management and clinical rehabilitation.

(c) Clinicopathologic: Our data are in keeping with the clinicopathologic concept that cirrhosis is induced by a combination of etiologic factors but not by any single cause. Equally important factors in the induction of

cirrhosis are the nutritional state of the liver cells, hepatic injury, and the ability of the liver to repair inflicted damage by regeneration. The possibility has been considered that auto-immunization against liver cell protein altered by injury may perpetuate the cirrhotic process despite removal of all injurious factors, but this speculation requires further careful studies.

ACKNOWLEDGMENTS

The author wishes to acknowledge the kind encouragement of Professor Ingle in the pursuit of this study. He gratefully appreciates the help and support given to him by Professor C. H. Best and associates during the greater part of this work which was performed in Toronto. He is particularly indebted to Professor Hamilton, Professor Hartroft, Professor Steiner and Professor Wissler for the many hours of discussion which were essential for the elaboration of the problems raised in this manuscript.

SUMMARIO IN INTERLINGUA

Duo sais mascule (i.e. simios del genere Cebus) de tres e cinque annos de etate serviva como lor proprie subjectos de controlo durante un periodo de observation preliminari de un anno e medie ante que illos entrava un curso de dieta cirrhogene de 17 menses de duration. Durante duo breve intervallos in le curso de ille 17 menses le sais recipeva un complete e nutritive dieta pro prevenir lor morte. Le dieta cirrhogene esseva magre in proteina, libere de cholina, e ric in cholesterol (2%). Ambe animales disveloppava un precoce cirrhosis del typo Laennec. Usque nunc, nulle altere methodo ha succedite a producer cirrhosis in simias.

Post que le diagnose esseva establite per laparotomia e histopathologia, le animales recipeva un regimen de plen valor nutritive como essayo therapeutic durante un periodo de novem menses. Le hypertension, le ascites, e le ictero dispareva. Le condition clinic e le apparentia grossier del hepate del animales se meliorava considerabilemente, sed intra le mentionate periodo le tableau histologic non poteva esser restaurate a un stato normal. Determinationes del proteina seral monstrava un inversion del proportion de albumina a globulina, e isto persisteva in despecto del melior tractamento therapeutic e de rehabilitation clinic.

Le datos es de accordo con le conception clinico-pathologic que cirrhosis es inducite per un combination de factores etiologic e non per un sol causa specific. Factores de importantia equal in le induction de cirrhosis es le stato nutritional del cellulas hepatic, le presentia de lesiones hepatic, e le capacitate unic del hepate de reparar injurias que illo ha suffrite per medio del regeneration de cellulas. Auto-immunisation contra le proteina del cellulas hepatic le qual ha essite alterate per le injuria es possibilemente responsabile pro le perpetuation del processo cirrhotic in despecto del elimination de omne factores nocive.

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CHLOROQUINE PHOSPHATE (ARALEN) IN THE LONG-TERM TREATMENT OF RHEUMA-TOID ARTHRITIS*

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This report describes the results obtained in a group of 50 consecutive private patients with chronic rheumatoid arthritis who received chloroquine phosphate (Aralen) as the major medical agent in the management of their disease for 18 to 36 months. The average duration of treatment was 24 months. An analysis of the successes and failures in this group will be presented with the clinical, laboratory and radiological changes that occurred during treatment. A dose schedule was evolved which was found to give the best results to the greatest number of patients with the least incidence of side effects.

During an intensive investigation of anti-malarial compounds, it was noticed that some of the patients in the study who happened to have rheumatoid arthritis showed an improvement in their arthritic symptoms. This led to a short term study of the effect of four antimalarial compounds on a group of 38 arthritic patients.¹ Some benefit was found in 23 of them. Several other studies have been reported since then. All of these have included patients who were treated for less than a year or who received steroids at the same time. The present study is made up of patients who were treated with chloroquine for 18 to 36 months and who had not received regular doses of steroids or phenylbutazone during the 12 months prior to the evaluation of results. This study was stimulated by Dr. Thomas McPherson Brown ² and Dr. Stuart Bush of George Washington University who recommended the use of chloroquine to the author in 1955.

METHODS AND CLINICAL MATERIAL

Only those patients who fulfilled the criteria of "Definite Rheumatoid Arthritis" according to the standards adopted by the American Rheumatism Association and whose disease had been continuously active for longer than a year were included in this study. Patients with disease of short duration were excluded in order to be as sure as possible that the results obtained were due to treatment and not to spontaneous fluctuation of the arthritis. Most of the patients were self referred or referred by other specialists. Only one was referred by a general practitioner. They probably represent a typical sample of cases of chronic rheumatoid arthritis seen in the average office practice. They were managed like any other private

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patients and did not receive free medication or services, except for extra tests and x-rays made at the end of the project.* The average duration of arthritis prior to chloroquine therapy was nine years with a range from two to 40 years. The duration of continuous activity averaged six years and ranged from one year to 27 years. The average age was 50 and ranged from 27 to 84 years. Forty-one were females and nine were males.

X-rays were taken at the start of treatment of the joints which were symptomatically the most troublesome. These included x-rays of the hands in 30 cases, 29 of which showed abnormalities of varying degrees. X-rays were taken of the hands in every case at the end of the period of evaluation. Abnormalities were found in 47 of the 50 patients.

Designations of the "Stage" of the disease and the "Class" of functional impairment were made according to the criteria of the American Rheumatism Association. † In 17 mild cases judged clinically to be Stage I, there were x-ray signs of slight to moderate cartilage thinning and/or sub-chondral bone destruction. This discrepancy arose because none of these cases were truly "early" since all cases of less than one year's duration had been excluded. The general clinical picture of these patients was much closer to Stage I than to Stage II and they are included in Stage I.

CHLOROQUINE ADMINISTRATION

At the beginning of this project, the effect of chloroquine on arthritic patients when used over a prolonged period of time was an unknown quantity. It was known that it could produce toxic reactions of moderate to severe degree when used in large doses for the treatment of malaria or hepatic amebiasis. Therefore, in the first patients treated, the extremely low dose of 62 mg. (one fourth of the usual 250 mg. tablet) was given three times a week for a weekly dose of 186 mg. This dose was well tolerated by all but one patient and was slowly increased.

Because the starting dose of 186 mg. a week was well tolerated by most patients, those started on chloroquine later in the study were begun on a dose of 125 mg. three times weekly. The experience gained with these and

*These and other expenses of preparing this report were financed in part by a grant-in-aid from Winthrop Laboratories, Inc.

† STAGE OF DISEASE ACCORDING TO ARA CRITERIA:

Early (no destructive changes radiologically). Stage I Stage II Moderate (slight cartilage or bone destruction without joint deformity). Stage III Severe (cartilage and bone destruction with joint deformity).

Stage III Severe (cartilage and bone destruction with joint deformity). Stage IV Terminal (bony or fibrous ankylosis).

CLASSIFICATION OF FUNCTIONAL IMPAIRMENT ACCORDING TO ARA CRITERIA:

Class I

Ability to carry out all usual duties without handicaps.

Ability adequate for normal activities despite discomfort or limited Class II joint motion.

Class III Ability to perform only few or none of the duties of usual occupation or self care.

Class IV Largely or wholly incapacitated, able to perform little or no self care.

subsequent patients has led to a schedule of more rapidly progressing, gradually increasing doses as shown in table 1. The patient is gradually advanced from one step to the next as his chloroquine tolerance will permit. When a dose was reached that produced a satisfactory rate of improvement, this dose was maintained indefinitely. The goal of therapy was to begin to achieve some subjective and objective improvement during the first three to six months of treatment while keeping the incidence of side effects at a minimum. If this was accomplished, continuation of the same dose of chloroquine was usually found to lead to good symptomatic relief in another six months. If symptomatic relief was not complete after six months on a dose that had at first produced an improvement, the dose was raised to the next level for another six months. In each group of patients raised a step in the dose schedule, some individuals developed symptoms of chloroquine intolerance. Therefore, all increases in dose were made slowly and cautiously. Using this plan of administration of chloroquine, two patients

TABLE 1
Chloroquine Dose Schedule

| Total Weekly Dose in mg. | Method of Administration | Usual Time on This Dose |
|-----------------------------|--|--|
| 93 to 187 | 31 or 63 mg. at bedtime Mon., Wed. and Fri. | Used only if patient is intolerant to 375 mg. a week |
| 375 | 125 mg. at bedtime Mon., Wed. and Fri. | 2 to 13 weeks |
| 750 | 250 mg. at bedtime Mon., Wed. and Fri. | 4 weeks or indefinitely |
| 1,500 | 250 mg. at bedtime every night except Sunday | 8 weeks or indefinitely |
| 2,250 | 500 mg. at bedtime Mon., Wed. and Fri. and 250 mg. at bedtime Tues., Thurs. and Sat. | 12 weeks or indefinitely |
| 3,000 | 500 mg. at bedtime every night except Sunday | Rarely increased beyond this dose |

had a complete remission after a year on 375 mg. a week. In 21 patients the maximum required dose was 750 mg. a week, in 26 the maximum dose was 1500 mg. a week and one patient required 3,000 mg. a week.

Toxic Reactions: When chloroquine was administered according to the dose schedule shown above, toxic reactions were infrequent, mild and easily reversible. Eight patients in this series showed signs of mild toxicity. Six of them were able to continue chloroquine, but one was unable to tolerate more than 186 mg. a week. The other five eventually had a good response to therapy.

The severe and dangerous toxic reactions found by Cohen and Calkins busing initial doses of 3,500 mg. a week have not occurred in any patients. It seems probable that the patients in this series who were sensitive to chloroquine, and likely to have dangerous reactions from large doses, were detected by their much milder toxic reactions to small doses. A detailed discussion of chloroquine tolerance will be given in another report now in preparation.

Duration of Treatment after a Remission Occurs: It is not possible to state definitely at this time how long chloroquine should be continued after a remission is obtained. Two patients in this series discontinued the drug three to six months after a complete remission. Both of them had a mild relapse within a year and are now under treatment again with good results. All patients are now advised that they should continue chloroquine for a year after all symptoms have been relieved and all objective signs of rheumatic activity have returned to normal. There have not been any instances of premature discontinuation of chloroquine since these criteria have been explained to the patients. More experience is needed before it is established how effective this additional year of therapy will be in protecting patients against relapses.

SUPPLEMENTARY MEDICATIONS

Since the effect of chloroquine therapy was usually slow, various methods of symptomatic relief were offered the patients at the beginning of therapy. Salicylates and analgesics combined with muscular relaxants were of help to many patients. If there was severe discomfort or disability and no contraindications to its use, the patient was offered phenylbutazone. patient thought the expense of the drug, the extra blood counts and the extra office visits were worth the expected relief, phenylbutazone was prescribed at starting doses of 600 to 800 mg. daily for four days. Thereafter, the dose was reduced as fast as possible. Phenylbutazone was given to 17 of these patients with worthwhile relief in 14. No patient needed to take phenylbutazone for more than six months after chloroquine was started, and only three patients needed it for longer than three months. No enhancement of toxic reactions was found to occur as a result of the combined administration of phenylbutazone and chloroquine according to the methods described in this study. One patient developed a skin rash from phenylbutazone but was able to continue chloroquine with no difficulty.

Steroids were not usually prescribed except for short term conditions. Six patients received single injections of intra-articular steroids for persistent swelling and discomfort in isolated joints or for traumatic flare-ups. Four patients received systemic steroids for rheumatoid arthritis. In two cases steroids had been prescribed previously by other physicians and were discontinued after two or three months of chloroquine therapy. Prednisone was prescribed in desperation for two patients with a poor response to all other forms of therapy, but its use was discontinued after one to two months of inadequate response.

ADJUNCTIVE THERAPY

Several types of adjunctive therapy were used which appeared to enhance the effectiveness of chloroquine. Infected foci, allergies and other physical conditions which aggravate arthritis were treated wherever practical. Ten patients harbored *Entamoeba histolytica* which were eliminated with Milibis or Camoform. In four of these cases, the arthritis improved to an appreciable extent after such treatment. Simple home physiotherapy, such as hot water baths for relaxation of stiff muscles and gentle stretching exercises for limitation of joint motion, was advised. Formal physiotherapy as such was not used, except in six patients who received ultra sound therapy with very good results after a traumatic "flare-up" of isolated joints. Emphasis was placed on the benefits of intermittent activity with short periods of rest. Patients were encouraged to maintain strength and mobility but not to exhaust themselves or flare-up the disease. Continuous attention was



Fig. 1. The right middle finger of a 32 year old female who started chloroquine in June, 1956. Note the decrease in osteoporosis. The other patient with improvement in osteoporosis showed similar changes after 30 months of treatment.

directed toward educating the patient to manage his own disease and toward maintaining a good physician-patient relationship. The patient was assured that the physician was concerned about the long term results as well as the present discomfort. The physician made it clear that although discomfort might be present for some months, disability could probably be prevented.

RESULTS

The response to therapy was graded according to the criteria of the American Rheumatism Association with some additional stipulations.

The designation of Grade I response was used for patients with complete remission of all objective signs of rheumatic activity, including a normal sedimentation rate. No patient was included in Grade I who needed to take any amount of aspirin regularly. Grade II response included those patients with major improvement and resolution of significant signs of inflammation such as joint redness, heat, or more than slight tenderness. No patient was included in Grade II who required more than six aspirin daily. Grade III response included patients who had significant decrease in discomfort, with increase in work tolerance and grip strength, but whose total improvement was judged as less than satisfactory by either the patient or the physician. Grade IV included patients whose deformities due to rheumatoid arthritis increased or whose general condition remained unchanged. A decrease in

Table 2

Grade of Clinical Response with Chloroquine Treatment from 18 to 36 Months
(Average Treatment 24 Months)

| | | A.R.A. Grade of Response | | | | | | |
|--|-----------------------|----------------------------------|----------------------------------|-----------------------------------|--|--|--|--|
| A.R.A. Stage of Disease at Start of Treatment | Number of Patients | Grade I Complete Remission | Grade II Major Improvement | Grade III Minor Improvement | Grade IV No Change or Regression | | | |
| Stage I—Mild cases | 18 | (67%) | (33%) | 0 | 0 | | | |
| Stage II—Obvious x-ray and clinical changes | 23 | (39%) | (57%) | 0 | (4%) | | | |
| Stage III—Joint deformities | 8 | (12%) | (36%) | (12%) | (36%) | | | |
| Stage IV—Ankylosis of joint | 1 | 0 | 0 | (100%) | 0 | | | |
| Total all Stages | 50 | 22 (44%) | 22 (44%) | (4%) | (8%) | | | |

sedimentation rate, increase in hematocrit, decrease of joint swelling or lack of progression of x-ray destruction did not influence the grading of the patients whose over-all clinical condition did not improve. Using these criteria the results were as shown in table 2. Four of the six patients with a poor response considered that the partial improvement they obtained from chloroquine was better than they had received from any other form of therapy. The improvement in these four cases consisted of resolution of anemia in one case, improvement in hematocrit in another, return to work in one and decrease in discomfort in all four. However, inadequate relief of symptoms or increase in deformities placed their response in Grade III or IV.

Changes in Laboratory Findings during Treatment: At the start of chloroquine treatment, 41 patients had an elevated sedimentation rate and

nine had values in the upper range of normal.* Twenty-one (51%) of the 41 patients with elevated sedimentation rates showed a return to normal values during treatment (table 3, Group A plus B). The average sedimentation rate of the 50 patients decreased from 23 to 13 during treatment, with a mean decrease of 10.2. The "t" test shows that this change is highly significant statistically (P < 0.01). Eight female patients had anemia due to rheumatoid arthritis at the beginning of treatment with hematocrits of 37 or less. Five of these (62%) became normal with hematocrits of 38 or more by the end of the treatment period. Two of the patients who did not return to normal showed an improvement of from 34 to 37 in one case and from 35 to 36 in the other. The average hematocrit of the eight anemic

TABLE 3

Changes in Sedimentation Rates and Hematocrits Before and During Chloroquine Therapy

| | Number of Patients | Wintrobe Corrected Sedimentation Rates | | | | Hematocrits | | | |
|---|--------------------------|---|------------------------------------|---------------------------|-----------------------|-------------|-------------------------------|--------|--------------------------|
| Group of Patients | | Normal at Start | Re- gressed to Ab- normal | Ab- normal at Start | Improved to Normal | | Regressed to Ab- normal | normal | Improved to Normal |
| Group A 13 month observation period before chloro- quine treatment | 31 | 6 | 3 50% of 6 | 25 | 8% of 25 | 24 | 3 12% of 24 | 7 | 3 43% of 7 |
| Group A 24 month treatment period with chloro- quine | 31 | 5 | 0 | 26 | 14 54% of 26 | 24 | 0 | 7 | 5 71% of 7 |
| Group B 24 month treatment with chloroquine, no observation period | 19 | 4 | 0 | 15 | 7 47% of 15 | 18 | 0 | 1 | 0 |
| Group A plus Group B 24 month treatment period with chloro- quine | 50 | 9 | 0 | 41 | 21 51% of 41 | 42 | 0 | 8 | 5 62% of 8 |

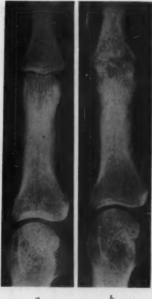
Normal sedimentation rates: Males—9 mm./hr, or less; females—13 mm./hr, or less. Normal hematocrits: Males—42 or more; females 38 or more.

patients increased from 35 to 40 during treatment, with a mean increase of 4.6. This change is highly significant statistically (P < 0.01). The results are considered to be clinically significant since no hematinic agents of any kind were used in the treatment of this series. This improvement in sedimentation rates and hematocrits seldom occurred in less than six months, and in some cases 24 months of therapy were required to bring about a return to normal values.

Thirty-one of the patients had been under observation while being treated with other methods for an average of 13 months before chloroquine

^{*}The ARA diagnostic criteria do not require the presence of an elevated sedimentation rate as long as other clinical criteria are present.

was used. This subgroup of 31 patients is designated as Group A in table 3. The changes in the hematocrits and sedimentation rates that occurred during this observation period can be compared with the changes that occurred in the same 31 patients during treatment with chloroquine. During the observation period of 13 months the average sedimentation rate had decreased slightly from 30 to 28. During the period of treatment with chloroquine averaging 24 months, the average sedimentation rate had decreased from 28 to 15. There was also a marked difference in the behavior of the hematocrits during the observation period and during the treatment



8/31/55

b 10/13/58

Fig. 2. The left index finger of a 45 year old female typist who began chloroquine in April, 1956. This is the only patient who developed deformity while taking chloroquine. Occupational trauma probably contributed to the damage.

period as shown in table 2. Group B in table 2 includes 19 patients who received chloroquine from the start of their treatment and did not have a period of observation before chloroquine. Improvement in sedimentation rates and hematocrits has been reported by other workers in chloroquine treated patients. Bagnall ⁶ reported a significant decrease in sedimentation rates in his patients with a Grade I, II and III response, but did not give percentages. Haydu ⁷ stated that sedimentation rates and hematocrits "showed improvement" but did not give figures.

Changes in Joint Measurements and Rheumatoid Nodules: Ring sizes were taken at the start of treatment in 16 patients selected at random who

had moderate to marked swelling of the finger joints. Fifteen of these patients showed a decrease ranging from 5 to 35 sizes with an average decrease of 12 sizes. One patient with extensive hypertrophic changes showed no change in ring size. At the beginning of treatment, there was significant limitation of joint motion in 45 patients. At the end of the treatment, three of these cases had even more limitation of motion in one or more joints. The other 42 cases showed improved mobility with return to completely normal motion of all joints in 22 cases. Of the 41 patients in Stages I and II who did not have deformities prior to therapy, only one patient developed a deformity. At the beginning of treatment 32 of the patients had joint effusions of varying amounts. During chloroquine therapy the effusions were eliminated in 11 cases, decreased in 20 cases and unchanged in one. Rheumatoid nodules were present in 14 patients at the beginning of chloroquine therapy. During treatment these disappeared in four cases, decreased in nine and increased in size in one case. During treatment with

Table 4
Change in Class of Functional Impairment During Chloroquine Treatment

| A.R.A. Functional Class before Treatment | Number of | Functional Class after Treatment | | | | | |
|---|-----------|----------------------------------|----|-----|----|--|--|
| A.K.A. Punctional Chass before Treatment | Patients | I | II | 111 | IV | | |
| Class I—Complete functional capacity | 0 | 0 | 0 | 0 | 0 | | |
| Class II—Functional capacity adequate but with discomfort | 39 | 32 | 7 | 0 | 0 | | |
| Class III—Capacity to perform few or no normal activities | 8 | 6 | 1 | 1 | 0 | | |
| Class IV—Incapacitated, wheel chair or bedridden | 3 | 1 | 0 | 1 | 1 | | |
| Total | 50 | 39 | 8 | 2 | 1 | | |

chloroquine 41 patients showed improved functional capacity of sufficient magnitude to improve their functional class by one to three classes according to the criteria of the American Rheumatism Association. Eight patients showed an improvement in function which was not sufficient to change their class. One patient showed a decreased functional capacity, but stayed within Class II. These results are shown in table 4. The ARA designation of stage of disease is made largely on the basis of x-ray and structural changes that are practically irreversible. One patient showed regression from Stage II to Stage III; the others did not change.

X-ray Changes: X-ray of the hands taken at the start of treatment were compared with those taken at the end of the study period in 30 cases. The average time between the pre-treatment and the final x-rays was 24 months. The films were compared for changes in porosis, erosion and deformities by the author, by an independent radiologist and by an independent rheumatolo-

gist. The entire series of 30 sets of films was reviewed twice by the author and the radiologist.* Then all films suspected of showing any change were reviewed by the independent rheumatologist, whose opinion was taken as final. The only changes considered to be significant were those found definitely to be present to the satisfaction of all three observers.

Two cases (7%) were considered improved radiologically as there was definitely less osteoporosis after treatment than before. These two patients had received chloroquine for 30 months in one case and for 27 months in the other. In 23 (76%) of the cases there were no definite changes. In four



3/6/56 3/4/58 3/17/59

Fig. 3. The third and fourth right fingers of a 74 year old male who has received chloroquine since June, 1956. There is progression of erosion between a and b during the first 20 months of treatment. There is little change between b and c during the next 12 months of chloroquine therapy. The progress of the erosion appears to have stopped. This patient continues to improve slowly after three years of chloroquine therapy.

cases there were increased areas of erosion and/or osteoporosis. One case showed an increase in ulnar deviation without other changes. Therefore, five cases (17%) showed radiological evidence of regression.

Clinical and Laboratory Findings Associated with a Good and a Poor Response to Chloroquine Therapy: Several clinical and laboratory findings were analyzed to see how the 44 patients (88% of 50) † with a good response of Grade I or II differed from the six patients (12% of 50) who had a poor response. These findings are shown in tables 2 and 5. The findings as-

^{*}The author is indebted to Dr. Lawrence A. Mucci whose continuous collaboration for the last five years has made this portion of the study possible.

†95% confidence limits 73 to 95% good response or 5 to 27% poor response.

TABLE 5

Correlation of Clinical Findings at the Start of Chloroquine Therapy to the Grade of Response to Treatment

| | | Grade | or Kesp | Olise to | 1 reatme | II C | | | |
|--|---------------------------------|----------------|-----------------|--------------------------|---|--------------------|---|-------------------------|-------------------------|
| | | at the Sta | | | Presence of Anemia Due to Rheumatoid Arthritis | | | | tion of otoms |
| A.R.A. Grade of Response | Less than 40 | 40 to 60 | More than 60 | Longer than 1 year | Less than 1 yr. | Previous anemia | Never anemic | Less than 5 years | More than 5 years |
| Grade I Complete remission 22 patients | 6 | 14 | 2 | | 2 | 2 | 18 | 9 | 13 |
| Grade II Major improvement 22 patients | 3 | 9 | 10 | 1 | 1 | 2 | 18 | 6 | 16 |
| Grade III Minor improvement 2 patients | | 1 | 1 | | | | 2 | 1 | 1 |
| Grade IV Regression 4 patients | | 1 | 3 | 4 | | | | 3 | 1 |
| Total group 50 patients | 9 | 25 | 16 | 5 | 3 | 4 | 38 | 19 | 31 |
| A.R.A. Grade of | Received Phenyl- butazone | Had | | lass of Fu Disabil | nctional lity | Wintro | Wintrobe Corrected Sedimentation Rate at Start of Therapy | | |
| Response | or Steroids | Nodul Nodul | | | Class IV | 13 or Less | 14 to 30 | 30 to 39 | 40 or More |
| Grade I Complete remission 22 patients | olete remission | | 4 | 0 | 6 | 10 | 4 | 2 | |
| Grade II Major improvement 22 patients | 4 | 4 | 19 | 2 | 1 | 2 | 9 | 7 | 4 |
| Grade III Minor improvement 2 patients | 1 | 1 | 1 | 0 | - 1 | i | 1 | 0 | 0 |
| Grade IV Regression 4 patients | 4 | 4 | , | 2 | 1 | 0 | 1 | 1 | 2 |
| Total group 50 patients | 17 | 14 | 39 | | 3 | 9 | 21 | 12 | 8 |

sociated with a good response and the rate of success in these groups were: age of less than 40 years (100%), absence of deformity (98%), Functional Class II (95%), and a normal hematocrit within the year before treatment was started (96%). The findings associated with a poor response and the failure rate for the groups of patients exhibiting them were: rheumatoid anemia of more than one year's duration (80%), presence of rheumatoid

nodules (36%), deformed joints (62%), Functional Class III or IV (36%), and discomfort severe enough to warrant the use of phenylbutazone or steroids (29%). The use of appropriate statistical tests (the Chi square or binomial confidence limits) showed that the associations were highly significant (P < 0.01) with respect to the presence or absence of a prolonged anemia, age of less than 40 and the presence of rheumatoid nodules. The tests showed a significant relationship (P < 0.05) with respect to the other findings mentioned above.

An apparent paradox is found with respect to the duration of the disease prior to treatment where it is seen that four of the six patients with a poor response had a shorter duration of symptoms prior to treatment than did the group as a whole. The explanation of this peculiar finding is that in each of these four patients the disease was getting rapidly worse in the three years just prior to chloroquine therapy and refractory anemias and/or deformed joints had developed during the relatively short course of their disease.

When the results were analyzed with regard to the Wintrobe sedimentation rate at the start of treament, only a very slight relationship was found. Nine patients had a normal sedimentation rate at the start of treatment. One (12%) had a poor response, which is the incidence of a poor response in the whole group. Only in those patients with a marked elevation of sedimentation rate of 40 mm. per hour or more was the response inclined to be different. More recent observations on these 50, as well as other patients, have shown that the Westergren sedimentation rate shows a much better correlation with the clinical degree of disease activity and the prognosis.

The maximum weekly dose of chloroquine that could be tolerated had a limiting effect on three of the six patients with a poor response. One could not tolerate a dose larger than 186 mg. a week and stopped treatment after 19 months of no response. In another case (figure 4) a mild intolerance to chloroquine limited the initial dose to 93 mg. a week. It required 88 weeks to persuade the patient to increase the dose gradually to 750 mg. a week. After this dose was finally reached, an improvement occurred. However, irreversible changes had taken place before then and she is classified as a Grade IV response. A third patient with a poor response took 750 mg. a week for 54 weeks, and 1,500 mg. a week for 23 weeks. Since the closing date of this project his dose has been increased gradually to 3,000 mg. a week and he has obtained a good response on this dose. The response to chloroquine therapy was also analyzed with respect to the race and sex of the patients and their age at the onset of the disease, but no significant correlation was found.

During the course of this study a total of 60 consecutive patients was started on chloroquine therapy. The results obtained in 10 of them could not be evaluated and are not included. Two stopped therapy because of



Fig. 4. The left second and third fingers of an 82 year old female with rapidly progressing disease of three years' duration when she started chloroquine in April, 1957. In a and b is shown the rapid progression of deformity and destruction which occurred in the 19 months before chloroquine, while she was receiving aspirin with small doses of steroids. In b and c is shown the less rapid progression of these changes in the 18 months of chloroquine therapy. More recent x-rays, taken in July, 1959, appear identical to c.

toxicity after taking the drug less than a month. Four moved out of the area and were lost to follow-up. One patient continued to take unnecessary steroids and phenylbutazone against advice and is not included in this study because it was impossible to evaluate the effect of the anti-malarial. Three others discontinued chloroquine after six to nine months of treatment because of good symptomatic relief. Two of these patients have had a relapse and are under treatment again with good results.

DISCUSSION

Three recently reported series of patients treated with chloroquine 6,7,8 have shown that the best results were obtained in patients whose disease had not progressed to the stage of joint deformity. These results are in agreement with this study and emphasize the need for early diagnosis and prompt institution of chloroquine therapy. A correlation between stage of disease at the beginning of treatment and the grade of response similar to that given in table 4 was found by Bagnall 6 who treated 108 patients for eight months to four years, and by Haydu 7 who treated 28 patients for six months. The data of these two workers have been rearranged according to stage of disease and grade of response so that the relationship is clearly seen in table 6. (These two tables have been reviewed by the authors and are published in this form with their permission.) Cramer's 9 group of 117 pri-

TABLE 6

Relationship of the Stage of Disease to Grade of Response in Previously Reported
Groups of Patients Treated with Chloroquine

| A.R.A. Stage of Disease at | Number of | | A.R.A. Grad | le of Response | |
|--|-------------------------|------------------------------|---------------------------|----------------------|--------------------------|
| A.R.A. Stage of Disease at Start of Treatment | Patients | Grade I | Grade II | Grade III | Grade IV |
| Treatment of pr | ivate patients for Dose | or 8 to 48 mo | nths (rearrange weekly | ed after Bagna | <i>ll</i> ⁶) |
| Stage I | 8 | 5 (63%) | (37%) | 0 | 0 |
| Stage II | 72 | 29 (41%) | 27 (39%) | (12%) | (8%) |
| Stage III | 28 | 5 (17%) | (28%) | (7%) | 13 (47%) |
| Stage IV | 1 | 0 | 0 | (100%) | 0 |
| Total all stages | 109 | 39 (36%) | 38 (35%) | 12 (10%) | 19 (17%) |
| Treatme | nt of private p | atients for 5 to 1,750 mg. u | lo 10 months (| Cramer®) | |
| Stage I | 33 | 13 (39%) | 15 (45%) | (6%) | 3 (9%) |
| Stage II | 75 | (19%) | 47 (63%) | 8 (11%) | (8%) |
| Stage III | 7 | (14%) | (14%) | (14%) | (57%) |
| Stage IV | 2 | 0 . | 0 | 0 | (100%) |
| Total all stages | 117 | 28 (24%) | 63 (54%) | 11 (9%) | 15 (13%) |
| Treatment | | 6 months (r. 1,500 mg. w | earranged after | Haydu ⁷) | |
| Stage I | 2 | . 0 | (100%) | 0 | 0 |
| Stage II | 14 | (7%) | 11 (78%) | (14%) | D |
| Stage III | 12 | 0 | (67%) | (25%) | (8%) |
| Stage IV | 0 | 0 | 0 | 0 | 0 |
| Total all stages | 28 | (3%) | 21 (76%) | 5 (18%) | (3%) |

vate patients treated four to 10 months shows the same tendency. A group of cases reported by Scherbel, Harrison and Atdjian from the Cleveland Clinic 10 also lends itself to this type of analysis but does not show the same correlation. Also, only 62% of their patients had a major improvement. These differences may be caused in part by the difference in the type of patients seen in a large referral clinic as opposed to the other four groups made up largely of private patients. Cohen and Calkins 5 recently published a short-term double blind study using high dosages of chloroquine for only 11 weeks. By using very precise methods of measurement which would detect the relatively small changes occurring in this short a period of treatment, they found improvement in either the ARA criteria or the Lansbury systemic index 11 in 90% of chloroquine treated cases, but in only 6% of placebo treated cases. Thus, in five previous reports and in the present series, definite improvement has been found in from 62% to 90% of the patients treated with chloroquine. These results compare very favorably with the results of long-term treatment with steroids. Bunim 12 had a Grade I or II response in 51% of 71 cases treated six to 48 months with cortisone. Engleman et al.13 had similar results in 45% of 56 patients treated four to 38 months with cortisone.

Comparison of Results with Other Methods of Treatment: The changes in the laboratory findings shown in table 3 compare favorably with the study reported by Smyth and Clark. In their group of 20 patients with elevated sedimentation rates prior to treatment, only one returned to normal during five months of treatment with cortisone, one month of treatment with aspirin and five months with phenylbutazone. A long-term study by the Joint Commission of the Medical Research Council of Great Britain 15 found that in 54 cases with abnormal sedimentation rates, two of 27 returned to normal after three years of cortisone therapy and five of 27 returned to normal after three years of aspirin therapy. However, their normal was 20 mm./hr. Westergren which is definitely higher than the normal used in the present study. That study 15 also showed that there was no significant change in hemoglobin after three years of treatment with either aspirin or cortisone. There was improvement of the hemoglobin in their cortisone treated cases at the end of one year, but this improvement was not sustained at the two and three year evaluations.

There have been only a few reported series of long-term evaluation of rheumatoid arthritis with x-rays of the hands taken before and after long-term therapy of any type. Table 7 shows that in previously published long-term series the percentage of patients showing a progression of the destruction seen in serial x-ray films increases the longer the period of observation is extended. The progression of these changes had not been greatly influenced by therapy with cortisone, prednisone, prednisone, phenylbutazone, for aspirin. In the present series of cases the percentage showing progressive destruction by x-ray seems significantly smaller than these other series shown in table 7.

TABLE 7
Changes in Osteoporosis or Erosion in Serial X-Rays of the Hands

| Author | Type of | Months of | Number of | X-ray Change During Treatment | | | |
|---|-------------------------|-----------------------|-----------|-------------------------------|------------|------------|--|
| | Treatment | Treatment | Patients | Better | No Change | Regression | |
| Joint Commission ¹⁷ | Prednisone Cortisone | 12 | 27 24 | 0 | 67% 58% | 33% | |
| Copeman et al.18 | Cortisone | 24 | 20 20 | 0 | 60% | 42% | |
| Bollet and Bunim ¹⁸ Morrison and Kuhns ¹⁹ | Cortisone Various | 12 to 48 48 to 144 | 20 65 | 3% | 25% | 70% | |
| Young (present study) | Chloroquine | 24 | 30 | 7% | 76% | 17% | |

The inability of steroid therapy to prevent the development of erosion has been shown by Bollet and Bunim.¹⁸ All of their six patients who were free of erosions at the start of treatment developed them during therapy with cortisone even though the disease was well suppressed in five of these cases. The British Joint Commission ²⁰ found that patients without erosions developed them during 24 months of therapy in 11 of 15 cases treated with aspirin and in 10 of 15 cases treated with cortisone. In the present series of cases treated with chloroquine, pre-treatment x-rays were available on 16 patients who did not have erosions at the start of therapy. Only one of these patients developed an erosion during a period of treatment averaging 22 months as shown in table 8.

Clinical Pattern of Response to Chloroquine: It required prolonged periods of chloroquine administration for the benefits to reach their fullest extent. The results reported took many months or years to obtain, especially in patients with more advanced disease. Twenty-six of these patients received chloroquine for two years or more. Eighteen of them have taken the drug for over 30 months. None of the patients received maximum benefit from the drug until after a year of therapy, and some are still improving after three years of treatment. The first improvement noted consisted of decreased pain and stiffness after two to 12 months of treatment. Then the objective signs of disease, such as swollen joints and laboratory abnormalities, began to improve. However, after the objective signs of disease had decreased some symptoms persisted for several months even in

TABLE 8
Erosions Which Developed in Patients Who Were Without Them at the Start of Treatment

| Author | Type of Treatment | Months of Treatment | Number of Patients | Number of Patients Who Developed Erosions |
|--------------------------------|--------------------------|------------------------|-----------------------|--|
| Joint Commission ¹⁵ | Cortisone Aspirin | 24 24 | 15 15 | 10 (65%) 11 (74%) |
| Bollet and Bunimis | Cortisone Chloroquine | 12 to 48 24 | 6 16 | 6 (100%) |

the absence of objective evidence of active arthritis. Continued treatment was followed by more complete symptomatic relief. The four groups shown in tables 2 and 6 are apparently made up of similar types of patients. Inspection of these tables shows that in the present study and in the report by Bagnall 6 where treatment was carried on for several years, the percentage of patients with a Grade I response was much higher than was reported by Haydu 7 who treated his patient for only six months. The difference in response between Grade I plus II and Grade III plus IV was highly significant statistically (P < 0.01) in the present study and in that of Bagnall and of Cramer, but not in that of Haydu in which treatment was for a shorter period.

The patients with symptoms of more than five years' duration, those who had rheumatoid anemias of less than one year's duration or who were more than 60 years of age at the start of therapy were slower to show a good response. Patients in these groups showed a significantly poorer response after only 12 months of treatment, but after 18 to 36 months of treatment the differences disappeared or became insignificant (table 5). The amount of disease or "spread" also influenced the rate of response. Patients with widespread disease responded much more slowly than did patients with only a few joints involved.

The joints which showed the earliest improvement with chloroquine therapy were the ones that had been most recently involved. In the most patients, the joints which had been involved for the longest time were the last to improve. This is similar to the pattern of response found by Lansbury ²¹ in patients undergoing a spontaneous remission of their arthritis.

Minor transient relapses of symptoms were frequently observed while the patients were slowly improving on chloroquine. These could almost always be ascribed to some condition known to aggravate arthritis. Infections such as upper respiratory infections, prostatitis and bacillary gastroenteritis would produce relapses lasting two to 12 weeks even though the infections were vigorously treated. Relapses of shorter duration were brought on by overactivity, psychological stress and inclement weather. These transient relapses became less severe and less frequent after the beneficial effect of chloroquine became more complete and had endured for six to 12 months.

The improvement from chloroquine therapy is a quite different pattern of response from the dramatic improvement that occurs within a few weeks after steroids are begun, but then does not progress further and even regresses in many cases. This difference may be seen by comparing the changes in grip strength measurements taken over a period of months in the chloroquine treated cases with the same measurements in steroid treated cases. In a recent study by the Joint Research Commission ¹⁷ a group of 70 patients who had received cortisone for over a year had an average grip strength of 136. Grip strength measurements had not been

taken before cortisone was given. Thirty-five of the patients were changed to prednisone and the average grip strength increased to 178 in 12 weeks. However, in 24 weeks it regressed to 170 and at the end of a year had regressed to 156. The 35 patients who were continued on cortisone regressed slightly from 136 to 133 during the year. The average grip strength of 40 patients in the present chloroquine treated series was 180 when it was first measured after an average of 14 months of therapy. At the end of 24 months of therapy the average grip strength had increased to 210 and only one patient had shown a significant decrease in strength.

It is very difficult to make a fair comparison of results obtained in different series of patients. Most of the series treated by other methods and reported in the literature are collected from hospitals or clinics to which difficult cases are referred. The arthritis would be more severe in such groups than it was in the group of office patients who made up the present study. Despite the inherent differences between this group and other reported groups used for comparison, the higher percentage of improvement in the clinical, laboratory and x-ray results of this chloroquine treated group appears to be greater than would be expected to occur entirely because of differences between the groups. The revised diagnostic criteria of the ARA 22 with the new classification of "Classical Rheumatoid Arthritis" will help make such comparisons more accurate. As well as can be determined in retrospect, at least 20 of these patients fitted the criteria of classical rheumatoid arthritis and 14 of them (70%) had a good response. Regardless of comparisons, this report demonstrates the beneficial results obtained in a group of unselected consecutive patients treated over a long period of time with chloroguine.

SUMMARY AND CONCLUSIONS

Chloroquine was used as the main medical agent in the comprehensive management of 50 cases of chronic rheumatoid arthritis who had continuous therapy for 18 to 36 months. Eighty-eight per cent of the patients had a major improvement or complete remission, 4% had a minor improvement and 8% had no improvement or regression. Furthermore, this improvement has been sustained for as long as 36 months without evidence of recurrence of symptoms or weakening of grip strength such as occurs during long-term steroid treatment. Treatment with chloroquine was followed by a return to normal of sedimentation rates and hematocrits in a much higher percentage of patients than has occurred in series treated solely with antiinflammatory agents such as steroids, phenylbutazone and aspirin. improvement in both the sedimentation rates and the hematocrits was found to be highly significant statistically. The rate of bone destruction found in yearly x-rays of the hands appears to be significantly less than was found to occur in groups of patients treated by other methods. The clinical pattern of response follows a sequence similar to that found in patients undergoing a spontaneous remission of arthritis. These differences in the type of improvement following chloroquine therapy make it reasonable to postulate that chloroquine does not act simply as an anti-inflammatory agent, but slowly affects some more basic feature of the disease.

An individualized dose schedule for chloroquine was devised. When chloroquine was given according to this dose schedule side effects were minimal in number, minor in degree and reversible in character. Treatment with chloroquine is only one third to one half as expensive as treatment with steroids or phenylbutazone.

In order to obtain the full benefit of chloroquine treatment, its adminis-

tration must be continued for more than one and one half years.

SUMMARIO IN INTERLINGUA

Chloroquina esseva usate como le principal agente medical in le tractamento general de 50 consecutive casos de chronic arthritis rheumatoide in le routine de un practica private. Le diagnose esseva facite secundo le criterios del Association Rheumatologic American (A.R.A.), sed le presente serie include solmente patientes in qui le symptomas esseva presente continuemente depost un anno ante le initiation del curso de chloroquina. Le droga esseva usate continuemente durante inter 18 e 24 menses. Octanta-octo pro cento del patientes experientiava un major melioration o un remission complete, in 4% le melioration esseva minor, e in 8% nulle melioration o regression esseva effectuate. Nulle del patientes includite in iste serie habeva recipite steroides o phenylbutazona in le curso del sex menses precedente le evalutation del resultatos. Le melioration esseva mantenite in omne le casos sin evidentia de un recurrentia de symptomas o de un regression del fortia del sasir como illo occurre in le therapia perdurative a steroides. Le tractamento con chloroquina esseva sequite per un retorno a valores normal del sedimentation e del hematocrites in un multo plus alte procentage de casos que in un serie tractate exclusivemente con agentes antiinflammatori como steroides, phenylbutazona, e aspirina. Le grado del destruction ossee constatate in radiogrammas annual del manos pareva esser significativemente inferior a illo notate in gruppos de patientes tractate per altere methodos. Le phases del responsa clinic sequeva un ordine simile a illo trovate in patientes qui experientia un remission spontanee de lor arthritis. Iste aspectos distinctive del melioration que occurre post le uso de chloroquina rende plausibile le postulato que chloroquina non age simple- e exclusivemente como agente anti-inflammatori sed affice etiam lentemente un elemento plus fundamental del morbo.

Esseva elaborate un individualisate programma de dosage que comenciava con 125 mg, tres vices per septimana. Le dose es augmentate lentemente usque il occurre un melioration subjective o objective. Le majoritate del patientes exhibi un satisfacente melioration post 9 a 18 menses de un dosage de 750 a 1500 mg per septimana. Patientes in le plus avantiate stadios de arthritis respondeva plus lentemente, e certes continuava meliorar se lentemente post 3 annos del therapia. Con iste programma de dosage, le effectos lateral esseva pauco numerose, basse in grado, e reversibile in character. Le uso simultanee de phenylbutazona e de altere agentes que es communmente empleate in le tractamento de arthritis non pareva esser associate con ulle augmento del effectos lateral. Le tractamento con chloroquina costa inter un tertio e un medietate del costo de tractamentos con steroides o phenylbutazona.

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THE PLEURAL AND PULMONARY COMPLICA-TIONS OF RHEUMATOID ARTHRITIS *

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RHEUMATOID arthritis has for some time been considered to be a generalized disease involving many tissues and organs in addition to the joints, and the possible occurrence of pulmonary and pleural lesions is compatible with this conception. Occasional references to chest complications in chronic rheumatism are to be found in the early medical literature. 1-6 These, however, must be treated with reserve, in view of the confusion that existed in the classification of chronic arthritis and the prevalence of tuberculosis at that time, as well as the frequency of hypostatic pneumonia among immobile and debilitated subjects. Such early reports were those of Fuller 1 in 1860, who considered that pleurisy and even empyema were complications of "rheumatic gout," and Charcot 2 in 1881, who regarded pleurisy and chronic pneumonia as examples of the visceral involvement which occurred late in the course of rheumatoid arthritis. Bronchitis, phthisis and pneumonia were cited as complications of rheumatoid arthritis by Bannatyne,3 and further mention of the frequent occurrence of pleurisy was made by Jones 4 and McCrae.5 Whereas none of these authors claimed that such respiratory involvement was in any way specific for the disease, Still,6 in reporting the finding of pleural effusion at autopsy in three patients with juvenile rheumatoid arthritis, considered this to be an important feature in the differentiation of the juvenile from the adult form of the disease.

More recently, Baggenstoss and Rosenberg 7 found autopsy evidence of previous pleurisy in 22 out of 30 subjects with rheumatoid arthritis, and Rosenberg et al.8 considered that pulmonary complications constituted the most common cause of death in this disease. Fingerman and Andrus,9 in an autopsy study on 61 patients, found evidence of a marked fibrous pleurisy in 23, bronchopneumonia in 24, lobar pneumonia in eight and pulmonary tuberculosis in seven.

The occurrence of a pleural effusion and pericarditis in a patient with rheumatoid arthritis was reported by Fletcher and Lewis-Faning 10 in 1945, and diffuse radiologic changes in the lungs of a patient with Felty's syndrome were described by Ellman 11 in 1947. The latter patient was found at autopsy to have a chronic fibrosing bronchopneumonia, and this extra-articular manifestation prompted Ellman to introduce the term "rheu-

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matoid disease" in preference to "rheumatoid arthritis." Since then, Ellman and his colleagues ¹²⁻¹⁶ have reported several patients in whom they claim to have identified pulmonary lesions of a rheumatoid nature, and there have been many other reported cases in the world literature where the lungs and pleurae seem to have been involved in the rheumatoid process. ¹⁷⁻⁸² In many instances the findings were supported by histologic studies of autopsy or biopsy material, ^{12, 14, 17, 20, 23, 24, 26, 28, 30}, but others depended upon clinical and radiologic evidence alone.

Atypical pneumoconiotic lesions have been described by Caplan ⁸⁸ in coalminers suffering from rheumatoid arthritis, and have been further studied by Miall et al. ⁸⁴, ³⁵ and Gough et al. ⁸⁰ Such lesions have also been reported in patients with rheumatoid arthritis whose various occupations

exposed them to other dust hazards. 87-45.

Edge and Rickards 30 in 1957, in a review of the literature, collected 56 recorded examples of rheumatoid arthritis with lung or pleural involvement. Nevertheless, acceptance of the fact that such lesions are specifically part of the rheumatoid process has not been universal. Aronoff et al.46 in a study of 253 cases of rheumatoid arthritis in 1955, were unconvinced of the existence of such an entity as the "rheumatoid lung." They compared the radiologic and autopsy findings with those of a control group, and the only suggestive feature forthcoming was the more frequent occurrence of certain nonspecific pulmonary and pleural lesions in the patients with rheumatoid arthritis. A similar controlled study of 532 patients with rheumatoid arthritis conducted by the Empire Rheumatism Council 47 in 1950 contained no mention of pleural or pulmonary lesions. Reynolds and Short, 48 in discussing the systemic features of rheumatoid arthritis, considered pleuritis to be a rare manifestation, and made no mention of pulmonary lesions. On the other hand. Sinclair and Cruikshank. 49 comparing the results of autopsies on 90 patients suffering from rheumatoid arthritis with an equal number of control subjects, concluded that pleural lesions were twice as common in the rheumatoid group. Cruikshank 50 subsequently stated that pleurisy occurred as part of the rheumatoid process in 40% of cases.

While the occurrence of specific changes in the lungs and pleurae of patients with rheumatoid arthritis may not have been placed beyond scientific doubt, the association of certain radiologic appearances and autopsy findings with this condition has been described sufficiently often to justify such an

assumption.

THE PRESENT SERIES

In the two-year period January, 1956, to December, 1957, inclusive, 180 patients suffering from rheumatoid arthritis were referred to one of us (M. T.) at the Department of Physical Medicine from other medical clinics and wards of the Royal Victoria Infirmary. This series was comprised of 52 males and 128 females with an average age of 53 years (range, 18 to 78). They were studied with regard to the existence of pleural and pulmonary

lesions, and questioned about any previous chest illnesses. In addition, their hospital records were searched for any evidence of former respiratory complications.

Of the total series, nine patients were found to have or to have had a pleural effusion for which no cause other than the rheumatoid process could be discovered. Two of these patients (cases 8 and 9) also had parenchymatous lung lesions. The principal findings in the nine patients are shown in table 1. Eight were males and one (case 6) was a female. Their ages ranged from 40 to 63 years, with an average of 52 years. Other causes of a pleural effusion were excluded as far as was possible. In all nine, tubercle bacilli were absent from the sputum, the pleural fluid or both on direct examination and on culture. Two of the patients were bronchoscoped and no evidence of a bronchogenic carcinoma was found, and examination of the sputum or pleural fluid for malignant cells was negative in six. Pleural biopsy was performed on three patients and no evidence of

TABLE 1
Principal Clinical Features in the Nine Patients Suffering from Rheumatoid
Arthritis Complicated by Pleural Effusion

| Pt. No. | Sex | Age | Effusion Confirmed by Aspiration | Underlying Lung Lesions | L.E. Cells | Sputum and/or Fluid for T.B. | Sputum and/or Fluid for Malignant Cells | Bronchos- copy | Follow-up |
|------------|-----|-----|---|-------------------------------|------------|---------------------------------------|---|-------------------|-----------|
| 1 | M | 46 | Yes | None | Absent | Negative | Negative | Negative | 21 years |
| 2 | M | 40 | Yes | None | Absent | Negative | Negative | Not done | 14 months |
| 3 | M | 48 | Yes | None | Absent | Negative | Negative | Not done | 2 years |
| 4 | M | 50 | Yes | None | Absent | Negative | Negative | Not done | 2 years |
| 5 | M | 60 | No | None | Absent | Negative | Not done | Not done | 5 years |
| 6 | F | 63 | Yes | None | Absent | Negative | Not done | Not done | 3 years |
| 7 | M | 56 | No | None | Absent | Negative | Not done | Not done | 8 years |
| 8 | M | 51 | Yes | Nodules | Absent | Negative | Not done | Negative | 7 years |
| 8 | M | 56 | Yes | Fibrosis | Absent | Negative | Negative | Not done | 5 years |

tuberculosis or malignant disease was found. In the remainder, as in all nine, no evidence of neoplastic change has been forthcoming during the follow-up period. Repeated search for L. E. cells was negative in every case.

There was a further patient in whom parenchymatous lung changes were likely to have been rheumatoid in nature but in whom other possible causes were not excluded. It is our purpose to present the case histories of these 10 patients and to review the features of interest with reference to previously recorded examples of this association. The diagnosis of rheumatoid arthritis was based upon the clinical and radiologic appearances and a positive Rose-Waaler agglutination to a titer of 1 in 64 or higher.

PLEURAL EFFUSION WITHOUT PARENCHYMATOUS LUNG INVOLVEMENT

Emerson ²⁷ stated that pleural effusion without evidence of lung involvement in rheumatoid arthritis is a rare phenomenon. The second of the two

patients described by Fletcher and Lewis-Faning 10 had this complication: she presented with the appearance of acute rheumatoid arthritis, and during the course of her illness developed a pleural effusion and pericarditis. Both complications eventually resolved spontaneously, but the arthritis progressed to the chronic deformities characteristic of severe rheumatoid disease. Ellman and Cudkowicz, 18 in reviewing the pulmonary manifestations of the diffuse collagen disorders, described a series of patients one of whom, a woman with rheumatoid arthritis, developed bilateral pleural effusions in the sixth year of her illness. This was accompanied by an exacerbation of her joint symptoms and episcleritis. These authors also mentioned the occurrence of a chronic empyema in one of their patients; this could have arisen either as a consequence of infection of an existing effusion or as a manifes: ation of the diffuse suppurative lesions which may occur in rheumatoid disease.⁵¹ Emerson ²⁷ reported six patients with rheumatoid arthritis, five of them males, who developed a pleural effusion during the course of their illness. In two the effusion occurred shortly after the onset of the disease, and in the remainder it coincided with an exacerbation of the arthralgia. Care was taken to exclude bronchogenic carcinoma and tuberculosis, but although it was stated that no evidence of diffuse lupus erythematosus or polyarteritis nodosa occurred during the period of follow-up, no mention was made of a search for L.E. cells. Mason and Steinberg 32 described a series of patients with rheumatoid arthritis, of whom six had pleural effusion and four had parenchymatous lung lesions of undetermined cause. The patients with pleural effusion were all males, and in each the onset of the effusion was accompanied by an exacerbation of the arthritis. All resolved without specific therapy.

Of our nine patients with a pleural effusion, seven had no demonstrable parenchymatous lung lesion.

CASE REPORTS

Case 1. A 46 year old man, by trade a wagonwright, developed pains in his elbows, shoulders, hips and knees in December, 1955. This was diagnosed as rheumatic fever, and on treatment with salicylates and rest in bed he showed an initial improvement. He later relapsed and in March, 1956, was referred to the Royal Victoria Infirmary for further investigation. He was found to have signs of acute rheumatoid arthritis with spindling of the proximal interphalangeal joints of the fingers. Further bed-rest and salicylates were prescribed, and after a month his joint signs and symptoms subsided, apart from some residual stiffness of the left shoulder, and he was able to resume his normal activities. He then found that he was becoming increasingly breathless on exertion; there was no cough, sweating or chest pain. He again attended hospital and was admitted to a medical ward. No history of any contact with tuberculosis could be obtained.

The patient was of robust build and good color, and showed no evidence of weight loss. There was, however, a mild evening pyrexia of 99° F. on several occasions during his stay in hospital. Slight spindling of his fingers was still apparent, although there was no joint tenderness. There were signs of an extensive right-sided pleural effusion. There was no evidence of any cardiac disorder and no

peripheral edema; the blood pressure was 150/86 mm. Hg. There was no lymphadenopathy, hepatomegaly or splenomegaly.

Radiologic examination of the chest (figure 1) confirmed the presence of a right pleural effusion. Radiologic examination of the hands showed patchy osteoporosis.

Investigation of the blood was normal: hemoglobin, 16 gm. per 100 ml.; white cells, 9,500 per cubic millimeter; neutrophils, 72%; lymphocytes, 20.5%; monocytes, 7%; eosinophils, 0.5%; L.E. cells, absent; erythrocyte sedimentation rate (Westergren), 4 mm. in one hour.

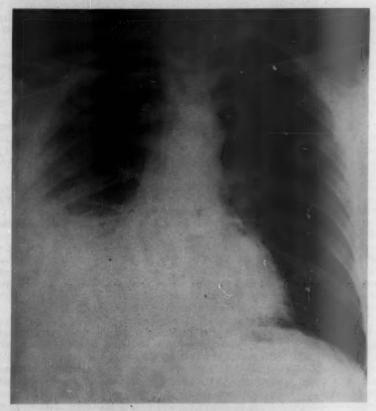


Fig. 1. Case 1. Right pleural effusion.

Paracentesis of the right pleural cavity was performed on several occasions, a turbid, pale yellow fluid being aspirated. This had a high protein content and a cellular exudate consisting of neutrophils, lymphocytes and giant cells. There were no malignant cells, and no tubercle bacilli were found on direct examination or culture. The sputum was also negative for tubercle bacilli on both direct examination and culture.

Further radiologic examination of the chest immediately after aspiration of the fluid revealed no abnormality of the lung fields. Bronchoscopy was performed by Mr. S. G. Griffin, and no abnormality of the bronchial tree was found.

The patient was discharged from hospital on June 16, 1956, and was seen at regular intervals as an out-patient. Further aspiration of the effusion was necessary one month and two months later, but since then it has not recurred, and the arthritis has also remained quiescent. A Rose-Waaler test in September, 1957, was positive to a titer of 1 in 256.

Case 2. A 40 year old male insurance agent was admitted to the Royal Victoria Infirmary on December 30, 1957. Apart from amebic hepatitis in 1943, he had been in good health until October, 1957. He then felt generally unwell and experienced aching pains in his shoulders, knees and ankles; he lost his appetite and began to lose weight. During the two weeks that preceded his admission to hospital he developed a cough, had attacks of sweating and shivering, and became increasingly short of breath.

The patient was flushed and looked ill, and had a temperature of 100° F. and a pulse rate of 100 per minute. There was slight clubbing of the fingers, and lymph nodes were palpably enlarged in both axillae, but no abnormality of his joints was detected at this time. There were signs of a moderately extensive pleural effusion on the left side. His liver was palpable two fingerbreadths below the costal margin, but there was no detectable enlargement of the spleen.

Radiologic examination of the chest confirmed the presence of a pleural effusion overlying the lower half of the left lung field (figure 2). The results of hematologic investigations were: hemoglobin, 12.6 gm. per 100 ml.; white cell count, 11,100 per cubic millimeter; neutrophils, 79%; lymphocytes, 16%; monocytes, 1%; eosinophils, 4%; erythrocyte sedimentation rate (Westergren), 30 mm. in one hour.

Paracentesis was performed and a turbid fluid obtained with a cellular content characteristic of an inflammatory exudate (neutrophils, 60%; lymphocytes, 40%). The protein content of the fluid was 4.3 gm. per 100 ml. No malignant cells were found in the pleural fluid or on repeated examination of the sputum, and no tubercle bacilli were found in sputum or fluid on direct examination and culture. The Mantoux test was positive to 1/10,000 dilution, agglutination against Brucella abortus was negative, and the antistreptolysin O titer was less than 50 units per milliliter. Plasma proteins were 5.5 gm. per 100 ml. (albumin, 3.2 gm.; globulin, 2.3 gm.), and electrophoresis showed some increase in gamma globulin. A biopsy of an axillary lymph node showed normal architecture, with evidence of activity of the germinal centers and some scarring, but no evidence of tuberculosis or neoplasia.

The patient was treated initially with penicillin and sulfamezathine, and frequent chest aspirations were performed. Five days after admission he began to complain of a return of his joint pain, which affected particularly his shoulders, hands, wrists and knees, and was accompanied by swelling and marked tenderness. Radiologic examination of both liands showed slight narrowing of the proximal interphalangeal joints, with some juxta-articular osteoporosis, consistent with early rheumatoid arthritis. A Rose-Waaler test was positive to a titer of 1 in 128, and C-reactive protein was strongly positive in the serum and pleural fluid. No L.E. cells were found in the peripheral blood.

There was little improvement on full dosage of salicylates, but when treated with prednisone in a dosage of 30 mg. daily the patient's joint symptoms were dramatically relieved. He was maintained on 20 mg. of prednisone and 40 gr. of calcium aspirin daily, and when discharged from hospital on February 26, 1958, two months after admission, a chest radiograph showed only residual pleural thickening at the left lung base. Since then there has been no recurrence of the effusion, but the arthritis has progressed to the changes of chronic rheumatoid disease.

Case 3. A 48 year old male patient, a plumber, developed an acute left-sided pleurisy with dyspnea and weakness in May, 1956. Over the next few weeks he lost 20 pounds in weight, and a radiograph of his chest revealed an effusion at the left

lung base. Paracentesis on two occasions produced 24 oz. and 16 oz. of clear, straw-colored fluid. Microscopic examination of the fluid and of the sputum failed to show malignant cells, and tubercle bacilli were also absent from both fluid and sputum on direct examination and culture. There was no history of contact with tuberculosis. The patient was treated with Pycamisan and advised to rest in bed.

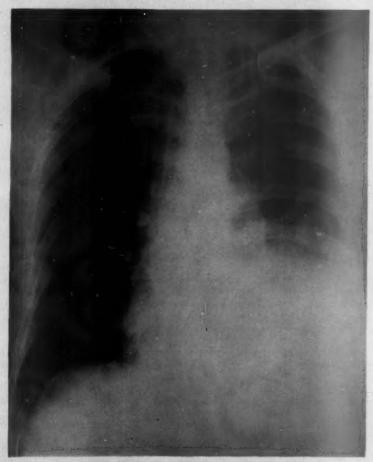


Fig. 2. Case 2. Left pleural effusion.

During the first week in June he developed a painful swelling of the right wrist and soft swelling of the tendon sheaths over the dorsum of the right carpus. Bursal enlargements at both olecranon regions and subcutaneous nodules near both elbow joints were noted. Morning stiffness, principally involving the lower limbs and lasting for two or three hours, was a prominent symptom. Further examination on July 11 showed that the effusion had resolved, and only slight residual pleural thickening was noted on the radiograph. The wrist swelling subsided following the ap-

plication of kaolin poultices, although the tendon swelling persisted. The patient felt well, and Pycamisan therapy was discontinued on September 19. In November, 1956, his right wrist became increasingly swollen and painful, and during the next three months his fingers, knees, left shoulder and ankles were intermittently involved. He complained then of malaise and anorexia. He was referred to the Royal Victoria Infirmary in January, 1957, at first to a surgical clinic, where his right wrist was immobilized in plaster; later, in July, 1957, he was transferred to the Department of Physical Medicine.

At this time the patient had the classic stigmata of rheumatoid arthritis in his hands, with spindle swelling of the proximal interphalangeal joints, swollen metacarpophalangeal joints, and soft swelling of the right extensor pollicis longus tendon. The left shoulder joint and both radiocarpal joints were also involved. Bilateral enlargement of the olecranon bursae was apparent, as were small nodules over both elbow regions. Radiologic examination of the hands and wrists revealed some osteoporosis in the small joints and a few small, subarticular erosions compatible with a diagnosis of rheumatoid arthritis. The chest radiograph at this stage showed no residual abnormality. The Rose-Waaler test was positive to a titer of 1/128, and the erythrocyte sedimentation rate (Westergren) rose to 28 mm. in one hour. L.E. cells were absent from the peripheral blood on repeated examination, and hematologic investigations were normal, as follows: hemoglobin, 14.9 gm. per 100 ml.; white cell count, 8,600 per cubic millimeter; neutrophils, 51%; lymphocytes, 44%; monocytes, 5%.

The patient was treated with calcium aspirin, 60 gr. daily, resting plaster splints and physiotherapy, and obtained a good remission of the arthritis. He is now at work in his usual occupation, and there has been no recurrence of the effusion two

years after its resolution.

Case 4. A 50 year old hairdresser became ill in August, 1956, with pain in the left side of the chest, cough, dyspnea and loss of weight. Radiologic examination on August 10 revealed a large left pleural effusion, and he was admitted to hospital. Just before admission he developed painful swelling of the metacarpophalangeal joints of both hands and of the left knee. His temperature on admission was 100.4° F., and subsequently never rose above 99° F. When he was seen by one of us (M. T.) in consultation, the clinical features were those of rheumatoid arthritis, and the signs of a left pleural effusion were confirmed.

The Rose-Waaler test was positive to a titer of 1/128; L.E. preparations were repeatedly negative, and the erythrocyte sedimentation rate (Westergren) was 35 mm. in one hour. The hemoglobin was 13.9 gm. per 100 ml.; plasma proteins, 7.0 gm. per 100 ml. (albumin, 3.5 gm.; globulin, 2.5 gm.). No tubercle bacilli were found in the sputum or pleural fluid on direct examination and culture, and no malignant cells were found. C-reactive protein was present in both serum and pleural fluid. Needle biopsy of the pleura (Dr. P. O. Leggatt) showed no evidence

of tuberculosis or malignancy.

On a basic régime of rest, the use of plaster splints, physiotherapy and calcium aspirin, 60 gr. daily, the patient's arthritis improved considerably. The pleural effusion recurred after repeated aspiration, and at present there is still radiologic evidence of gross pleural thickening and encysted fluid on the left side, but no evidence of any intrapulmonary lesion. Two and a half years after the onset of his illness he has only minimal residual signs of arthritis, and is at full-time work in his usual occupation. The erythrocyte sedimentation rate (Westergren) is 14 mm. in one hour.

Case 5. A 60 year old laborer developed acute left-sided pleurisy in March 1953, with chest pain, cough, yellow sputum, dyspnea and loss of weight. Within a week or two he developed acute polyarthritis, involving successively the right knee,

left shoulder and several small joints of the fingers and feet. He was referred to the Royal Victoria Infirmary and admitted to a medical ward on June 1, 1953, with a diagnosis of rheumatoid arthritis and right-sided pleural effusion.

The patient gave a history of three mild attacks of pleurisy in association with transient respiratory illnesses at the ages of 17, 33 and 51 years. Radiologic examination of the chest following the third attack was normal. He also gave a history of duodenal ulcer, and of severe psoriasis from the age of 16 years. Since the age of 39 his psoriasis had regressed, and at the time of his admission he had only minor residual patches over the scalp, trunk and elbows.

On admission the temperature was 99.4° F., and the erythrocyte sedimentation rate (Westergren) was 98 mm. in one hour. The chest radiograph confirmed the presence of an effusion in the right costophrenic region, without any apparent intrapulmonary lesion. Repeated sputum examinations and cultures were negative for

M. tuberculosis.

The patient was treated with rest and salicylates, and made satisfactory progress. Further radiographs of the chest showed progressive resolution and finally complete disappearance of the effusion by April, 1954. The arthritis, however, remained troublesome, and he was referred to the Department of Physical Medicine in June, 1956. He was treated with intra-articular hydrocortisone acetate, physiotherapy, resting plaster splints, salicylates and a course of gold injections, and made a satisfactory improvement. The erythrocyte sedimentation rate, which was 80 mm. in one hour (Westergren) before treatment, fell to 20 mm. in one hour, and the Rose-Waaler test, which was positive to a titer of 1/2048, fell progressively during gold therapy to 1/128. The only residual radiologic abnormality is pleural thickening down the right axillary border and in the region of the longitudinal fissure. The patient is now well and fit for work, but unemployed.

Case 6. A 64 year old housewife was admitted to the Royal Victoria Infirmary in May, 1955. She had suffered for 11 years from rheumatoid arthritis which had started in her hands and become generalized, and for 18 months before her admission she had been severely incapacitated. Three weeks before admission she developed a cough and a sharp pain in the right side of her chest, which was accentuated by coughing and breathing. For one week she had been troubled with diarrhea. Examination revealed a thin, pale woman with edema of the ankles and sacrum. She had gross rheumatoid changes in her hands, wrists, elbows and knees. There were physical signs of pleural effusion at both lung bases, especially on the right side. Her pulse rate was 72 per minute; blood pressure, 140/110 mm. of Hg; heart sounds, normal. Radiograph of the chest showed bilateral pleural effusions (more marked on the right), and also pathologic fractures of the seventh right and eighth left ribs.

The patient was grossly anemic: hemoglobin, 5 gm. per 100 ml.; red blood cells, 2.06 million per cubic millimeter; white cells, 3,700 per cubic millimeter; neutrophils, 78%; lymphocytes, 18%; monocytes, 3%; eosinophils, 1%. Blood calcium and phosphorus were low (calcium, 7.6 mg. per 100 ml.; phosphate, 1.0 mg. per 100 ml.). Alkaline phosphatase, 23.7 units (Jenner and Kay). Serum proteins were 6.8 gm. per 100 ml.; albumin, 3.2 gm.; globulin, 3.6 gm. There was radiologic evidence of osteomalacia and, although a five-day fat balance result was within normal limits, the anemia and biochemical abnormalities were thought to be due to steatorrhea. Sputum examination was negative for M. tuberculosis, and only pneumococci were obtained on culture. Culture of feces was likewise negative for M, tuberculosis. On chest aspiration one and one-half pints of straw-colored fluid were obtained from the right pleural cavity, and one-half pint from the left. Culture of the fluid for M. tuberculosis was negative. It contained 6 gm. of protein per 100 ml. Some neutrophils and lymphocytes were present, but no malignant cells were found.

For the first four weeks of the patient's hospital stay she ran an intermittent

pyrexia up to 104° F. This failed to respond to penicillin. She was treated by blood transfusion, intravenous iron and, later, iron by mouth, and vitamins A, C and D. She was also given digoxin and mersalyl, and repeated chest aspirations were performed. She was discharged from hospital two months after admission, and her chest radiograph showed that the effusion on the left had resolved, and that the one on the right was considerably less.

During the patient's re-admission to hospital in April, 1956, for a febrile illness, a chest radiograph showed some residual pleural opacity in both costophrenic angles. She was referred to the Department of Physical Medicine, which she has since visited regularly for treatment of her arthritis. L.E. cells have been repeatedly searched for and have not been found, and the Rose-Waaler test is positive to a titer of 1/256.

Although this patient had additional complications, due to presumed steatorrhea, it is felt that the pleural effusions were likely to be due to the rheumatoid process. The protein content was that of an exudate (6 gm. per 100 ml.), and not likely to have been due to congestive failure.

Case 7. A 56 year old male patient, a mine manager, had had an acute respiratory illness in November, 1950, with cough, dyspnea, chest pain of pleuritic type, and loss of weight. During this illness he noticed morning stiffness affecting his fingers. He returned to work after two weeks and found he could not lift heavy objects because of pain and stiffness of his hands. Three weeks later he developed acute arthritis of both elbows, and his knees also were involved. Since then he has had periods of comparative remission, but experienced sharp exacerbations of arthritis of his knees in 1953, hands, shoulders, elbows and ankles in 1955, and knees, ankles and wrists in 1957. He was referred to the Royal Victoria Infirmary in September, 1957, and transferred to the Department of Physical Medicine.

Examination revealed classic evidence of rheumatoid polyarthritis with, in addition, swollen extensor tendons at the wrists, and enlarged bursae and nodules over both olecranon regions. There was impaired movement of the right side of the chest on respiration, with other physical signs indicative of pleural thickening or effusion.

Radiologic examination of the chest showed gross pleural thickening in the right costophrenic and axillary regions, with possible encysted effusion. There was no evidence of any intrapulmonary lesion. Fluid was not obtained on attempts at aspiration. Repeated sputum examinations and cultures were negative for *M. tuberculosis*. Hematologic investigations gave the following results: hemoglobin, 13.32 gm. per 100 ml.; white cell count, 9,600 per cubic millimeter, with normal differential distribution; erythrocyte sedimentation rate, (Westergren), 95 mm. in one hour; L.E. cell preparations, negative. The Rose-Waaler test was positive to a titer of 1/1024.

The patient was treated with phenylbutazone, 300 mg. daily, calcium aspirin, 60 gr. daily, resting splints, physiotherapy and intra-articular injections of hydrocortisone acetate. He maintained a reasonably good functional level and was able to continue at work until July, 1958, when he was admitted to hospital with edema of the ankles and marked albuminuria. There were no casts or red cells in the urine, and the blood pressure was normal. There was no enlargement of the liver or spleen. Plasma proteins were 6.9 gm. per 100 ml. (albumin, 1.7 gm.; globulin, 4.3 gm., with an increase of γ and α_2 globulin). The blood urea was 27 mg. per 100 ml. The hemoglobin was 11 gm. per 100 ml., and the white cell count, 9,500 per cubic millimeter. The erythrocyte sedimentation rate (Westergren) was 125 mm. in one hour. L.E. cell preparations were repeatedly negative. The Congo red test was normal (46% of the dye remaining in the plasma after one hour), and liver biopsy showed no evidence of amyloidosis. The edema subsided spontaneously, and the patient was discharged after one month. He was readmitted four months later with a recurrence

of his edema and gross albuminuria. Plasma proteins were 4.3 gm. per 100 ml. (albumin, 0.9 gm.; globulin, 3.4 gm.) He was treated with triamcinolone, to which he made a good response, and he is at the moment free of edema, although albuminuria persists.

PARENCHYMATOUS LUNG CHANGES

1. Nodular Lung Lesions: The subcutaneous rheumatoid nodule has been described by Collins 52 and by Bennett and his colleagues. 53 Similar nodular lesions have been described as occurring in the lungs and pleurae of patients with rheumatoid arthritis, having been discovered at autopsy. 17, 14 In the case reported by Ellman et al.14 the pleura was grossly thickened with collagenous tissue and infiltrated with chronic inflammatory cells. Nodules were found in the adjacent lung tissue: they were characterized by a central necrotic zone, an intermediate zone of radially arranged elongated cells with pale nuclei and indistinct outlines, and an outer zone of chronic inflammatory cells, including numerous plasma cells. Nearby alveoli were collapsed, and there were interstitial fibrosis and subacute inflammatory change. Three patients with such nodular lung lesions were reported by Christie,24 who gave a detailed account of the autopsy findings. Nodules varied in size from small necrotic foci of 3 mm, diameter to one large round mass, 7 cm. across, demonstrated in the left upper lobe in the third patient. These lesions were said to be histologically indistinguishable from the characteristic subcutaneous rheumatoid nodule. The dense round nodule described in the third patient was demonstrable radiologically before death. Similar dense homogeneous shadows on the radiograph of the lung fields were described by Harris 22 in a patient with longstanding rheumatoid arthritis. The appearance of these shadows corresponded to an exacerbation of the joint symptoms, and the shadows were seen to diminish progressively over a period of three months. Nodular shadowing on radiographs of the chest in two patients with rheumatoid arthritis was described by Edge and Rickards. In each, lung biopsy revealed dense fibrosis of a nonspecific nature.

The nodular changes described by Caplan ³³ in the lungs of coalminers with rheumatoid arthritis have already been mentioned. He found that massive fibrosis was more common in miners who had rheumatoid arthritis, and in a quarter of these the radiographic opacities were of a peculiar type. They took the form of numerous, well-defined rounded shadows on a background of minimal pneumoconiotic change. Miall ³⁵ considered these lesions to be a reaction of rheumatoid tissue to irritant coal dust distinct from the response of normal lung. This pattern of reaction is not confined to coalminers, but can be seen in the lungs of rheumatoid patients whose occupations involve them in other dust hazards. It has been reported in silica workers, ⁸⁷⁻⁴¹ in a boiler scaler, ⁴⁸ in a foundry worker ⁴⁴ and in an asbestos worker. ⁴⁵

Nodular lung lesions can be accompanied by pleural effusion in patients

with rheumatoid arthritis. In Gruenwald's ¹⁷ patient at autopsy, in addition to nodules in the lungs, dense fibrous adhesions were found in both pleural cavities with pockets of encysted fluid. Such were the findings also in two of Christie's ²⁴ patients, and in one of the patients described by Ellman and his colleagues. ^{13, 14} In one of our patients with a pleural effusion, nodular lesions were present in the lungs.

CASE REPORTS

Case 8. A 51 year old coalminer developed rheumatoid arthritis in 1948. The onset was abrupt, both elbows, both wrists and the small joints of both hands being affected. Initially the arthritis progressed rapidly, but later he had a good remission.



Fig. 3. Case 8. Pulmonary nodule. High power view of the edge of the nodule, showing necrotic central area (top) with palisading of the nuclei. H. and E. \times 125.

During 1951 the patient developed a cough with a small amount of sputum, breathlessness on exertion, and progressive weight loss. There was no hemoptysis. Radiographs showed a right pleural effusion and nodular shadows in the right lung field. He was admitted to the Newcastle Regional Chest Surgery Centre at Shotley Bridge in February, 1952. There was evidence of rheumatoid arthritis in the form of swelling of the metacarpophalangeal joints and subcutaneous nodules on his forearms. Examination of his chest revealed some dullness to percussion and diminished air entry in the right axilla. Radiographic examination of the lungs demonstrated

a rounded mass in the right middle lobe, which was suspected of being a carcinoma. Bronchoscopy did not confirm this.

The following investigations were done: Sputum examination and culture, negative for *M. tuberculosis*. Hemoglobin, 106%; red blood cells, 5.2 million per cubic millimeter; white blood cells, 6,800 per cubic millimeter; erythrocyte sedimentation rate (Westergren), 22 mm. in one hour; urine, no abnormality; Wassermann reaction, negative.

A right thoracotomy was performed by Mr. G. A. Mason and a thick-walled interlobar effusion was found. This was aspirated and the wall excised. A small nodule in the apical segment of the lower lobe was accessible, and was removed for section.

The fluid removed at operation was found to contain some red and white cells but to be sterile on culture. The protein content was 5 gm. per 100 ml.

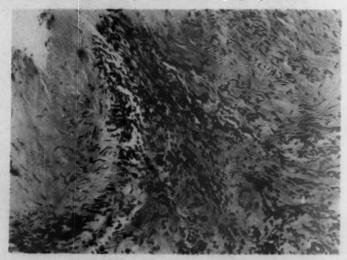


Fig. 4. Case 8. Pleura. High power view of pleura, showing necrotic collagen on left, with palisading of nuclei. H. and E. × 125.

The histologic sections of the lung nodule and the pleura are shown in figures 3 and 4. The nodule center was 1.3 cm. in diameter and was composed mainly of dense, hyalinized collagenous tissue, the central portion of which showed evidence of necrosis. Sections were prepared of the pleura and nodule, some of the latter being stained by the Ziehl-Neelsen method. These sections have been reported upon by Dr. I. Rannie as follows:

"The pleura shows great fibrous thickening with, on the outer border, a strip of hyaline necrotic collagen separated from the surviving tissue by a zone where there is typical palisading of nuclei (figure 4). The pulmonary nodule shows central hyaline necrotic tissue with, as in the pleura, a zone of palisading of nuclei between this and the surrounding tissue (figure 3). No tubercle bacilli were found in either the lung or pleura and the appearances are identical with those found in a rheumatoid nodule."

In 1954 the patient's chest radiograph showed that he had developed a left-sided pleural effusion. In January, 1956, when seen by one of us (M. T.), he was found

to have the classic appearances of rheumatoid arthritis. His Rose-Waaler test was positive to a titer of 1/128, and L.E. cells were absent. Radiograph of his chest (figure 5) showed a left-sided pleural effusion, and nodular shadows distributed about both lung fields.

2. Diffuse Lung Lesions: The patient reported by Ellman ¹¹ and the three by Ellman and Ball ¹² had lung lesions which the authors described as "chronic fibrosing pneumonitis." Transient diffuse shadowing on the radio-

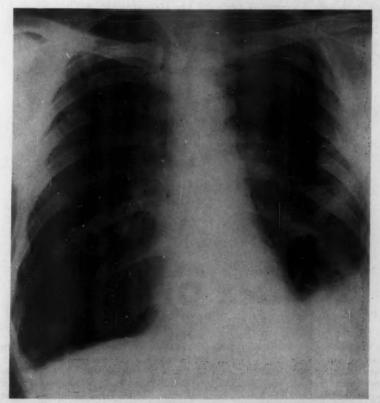


Fig. 5. Case 8. Left pleural effusion and diffusely scattered nodular lesions in both lungs.

graph of the chest of a boy with juvenile rheumatoid arthritis was reported by Leys and Swift.¹⁰ Yardumian and Kleinerman,²⁰ at autopsy on one of their patients, found that the lungs showed diffuse atelectasis and pneumonitis with perivascular round cell infiltration and hyaline thickening of the alveolar walls. Rubin ²⁵ described three patients, in two of whom lung biopsy had been performed. The radiographic appearances were of diffuse mottling of the lung fields with interstitial striations. Biopsy section showed fibrosis

of the alveolar septa and distortion of the alveolar spaces. Rubin and Lubliner ⁵⁴ have drawn attention to the resemblance of these lung lesions to those described by Hamman and Rich ⁵⁵ in four patients with "acute diffuse interstitial fibrosis of the lungs," an apparently nonoccupational pulmonary fibrosis occurring predominantly in middle aged men. Further examples have been reported of diffuse mottling of the lung fields shown on the radiographs of patients with rheumatoid arthritis. ^{16, 26, 30, 82}

These diffuse lung changes can also be accompanied by pleural effu-

sion.21,23 Such was the case in one of our patients.

Case 9. A 57 year old coalminer first attended hospital in March, 1953, complaining of painful swellings of the elbows, hands, shoulders and left side of jaw of three months' duration. A diagnosis of rheumatoid arthritis was made, and a radiograph of his chest taken at that time showed basal emphysema only. Later in 1953 he had two attacks of pneumonia, and has not worked in any capacity since.

He became increasingly dyspneic over the next two years, and lost about 28 pounds in weight. He was again admitted to hospital in April, 1955, and signs of a right-sided pleural effusion were discovered; this was confirmed radiologically. On thoracentesis, 16 oz. of pale yellow turbid fluid were obtained. This fluid contained lymphocytes and occasional neutrophils, and was sterile on culture. Repeated examination of the sputum for *M. tuberculosis* was negative. Investigation of the blood revealed: henoglobin, 11 gm. per 100 ml.; white cell count, 13,200 per cubic millimeter, of which 92% were neutrophils; erythrocyte sedimentation rate (Westergren), 93 mm. in one hour. The urine contained a small amount of albumin. The patient was considered to be too ill for bronchoscopy, but tomograms taken of the region of the bifurcation of the trachea and the right main bronchus showed no evidence of bronchogenic carcinoma or mediastinal lymphadenopathy. Biopsy of a palpable axillary lymph node showed only reactive hyperplasia.

The patient was referred to the Department of Physical Medicine early in 1957 when a radiograph of his chest (figure 6) showed a persisting right pleural effusion, and diffuse linear shadows throughout both lung fields compatible with extensive pulmonary fibrosis. These changes have advanced since then. The Rose-Waaler test was positive to a titer of 1/128, and repeated examination of the blood for L.E. cells was negative. Pleural punch biopsy (Dr. P. O. Leggatt) revealed no evidence of tuberculosis or malignancy. The patient has been treated with intra-articular

prednisolone, and his arthritis is no longer troublesome.

It is emphasized that a pleural effusion was discovered two years after this patient had left his job in the mines, and that diffuse pulmonary fibrosis did not appear until two years after that.

3. "Honeycomb Lung": "Honeycomb lung" is a descriptive term applicable to a particular radiographic appearance encountered in a variety of conditions—for example, tuberculosis, scleroderma, congenital cystic disease and saccular bronchiectasis. The honeycomb appearance is obviously not characteristic of any of these conditions; they may present radiographically, either as pure cystic lesions or as diffuse fibrosis without honeycombing. Aronoff et al. 16 recognized four cases of honeycomb lung in their series of 130 rheumatoid subjects in whom a chest radiograph had been done, and Dixon and Ball 28 have recorded the clinical, radiologic and pathologic features of this condition in a man suffering from rheumatoid arthritis who



Fig. 6. Case 9. Right pleural effusion and bilateral pulmonary fibrosis (May, 1957).

died of asphyxia. The histologic findings were those of a nonspecific interstitial fibrosis involving the bronchioles and their subdivisions, no lesions characteristic of rheumatoid disease having been recognized.

As one of our patients with rheumatoid arthritis showed the radiographic picture of "honeycomb lung," his case history is briefly presented.

Case 10. A coalminer, aged 51 years, developed acute and severe rheumatoid arthritis in November, 1950, and was subsequently treated with courses of ACTH and cortisone. He had no other illness or symptoms except a chronic suppurative otitis media. No radiograph of his chest was taken at this stage, but a mass miniature radiograph in 1948 had been reported as normal. While on cortisone he

developed symptoms characteristic of a duodenal ulcer, and this diagnosis was confirmed by barium meal examination. Subsequent repeated hematemeses necessitated surgical treatment, and a partial gastrectomy was performed (Professor A. G. R. Lowdon) in November, 1954. Postoperatively, the patient developed symptoms considered to be due to pulmonary collapse, and on the radiograph taken one day after operation the radiologist reported "infiltrations" in both lower lobes, with some collapse of the right lower lobe. Radiographs taken since the patient was referred to the Department of Physical Medicine have revealed a similar picture, the appearances being those of "honeycomb lung." In view of his poor general condition, no further investigations were performed. It is recognized that the present radiologic appearances could be due to aspiration pneumonitis and bilateral pulmonary collapse, with subsequent bronchiectasis and fibrosis, and the "honeycomb lung" in this instance may not be related to the rheumatoid process.

4. Pulmonary Vascular Lesions: The occurrence of pulmonary hypertension in a patient suffering from rheumatoid arthritis and, at autopsy, intimal sclerosis of the pulmonary arteries, has been recorded by Gardner et al.²⁹ These authors drew attention to the fact that similar vascular changes were noted in the digital vessels in their patient, who had suffered from peripheral vascular symptoms during life. This association of digital and pulmonary arterial involvement may occur as part of the general arteritis of rheumatoid disease, as described by Cruikshank,⁵⁶ and it is an association also seen commonly in scleroderma. Wade and Ball ⁵⁷ reported that some of their patients with idiopathic pulmonary hypertension consequent upon intimal sclerosis had a positive Rose-Waaler test in the absence of arthritis. We did not discover evidence of pulmonary hypertension in any of our patients, and from the paucity of reports on this subject it would appear that distinct pulmonary vascular lesions are rare findings in rheumatoid arthritis.

Discussion

It is not surprising that pleural and pulmonary complications should occur in patients suffering from rheumatoid arthritis. The respiratory tract contains a considerable amount of connective tissue, since the lungs have a large interstitial stroma, a profusion of blood vessels and a wide serosal area of pleura. All of these structures may be implicated in pathologic processes involving connective tissue. The pulmonary and pleural lesions reported in rheumatoid disease can be as variable in severity and chronicity as those in other situations, and can range from small or large acute exudative reactions to fibrotic lesions of loose or dense texture. This is typified by the changes found in the pleura, which may vary from small, localized fibrinous plaques consequent upon a mild attack of dry pleurisy, to extensive areas of dense pleural scarring, with chronic encysted and recurrent effusion, gross nodule formation, or even chronic empyema.

Connective tissue diseases other than rheumatoid arthritis may give rise to pleural and pulmonary lesions, as in scleroderma, polyarteritis nodosa, disseminated lupus erythematosus and dermatomyositis. Generally, the

respiratory lesions in these conditions consist of pleural or pulmonary fibrosis and, although certain patterns of reaction occur (more so in some of these diseases than in others), there is often no characteristic feature about the pathologic and radiologic appearances which would distinguish the pulmonary lesions of one connective tissue disease from those of another.

Scleroderma can produce widespread fibrotic changes throughout the lung fields, with irregular scarring and multiple small cyst formation, giving rise to the condition known as "honeycomb lung" (Getzowa ⁵⁸). As already stated, "honeycomb lung" has been reported in rheumatoid arthritis, ^{46, 28} and one of our patients (case 10) had radiologic evidence of this condition.

In disseminated lupus erythematosus, pleuritis and pleural effusion are not infrequent findings. In some of the earlier case reports, where pleural effusion was thought to complicate rheumatoid arthritis, the occurrence of other clinical features, such as a rash or multiple serosal involvement, raised the question as to whether the patients were in fact suffering from rheumatoid disease, or from disseminated lupus. Shaldon, 50 commenting on Emerson's 27 series, described a female patient with apparently typical rheumatoid arthritis and a pleural effusion who did not develop any further signs of disseminated lupus until five years later. In our nine patients with pleural effusion, repeated search was made for L.E. cells in the peripheral blood, and in all there were persistently negative results. Moreover, as all save one of the patients were males, and as other features of disseminated lupus (e.g., pericarditis, skin rash or leukopenia) were absent, such a diagnosis seems most unlikely. One of the patients (case 7) did, however, develop a nephrotic syndrome during the follow-up period, the cause of which remains obscure. This was not accompanied by a skin rash or leukopenia, and red cells were absent from the urine. His joint changes were characteristic of classic rheumatoid arthritis, and were accompanied by tendon lesions and nodule formation. As the nephrotic syndrome developed eight years after the arthritis, the likelihood of its being due to disseminated lupus seems to be remote.

The question as to whether there is a state in which patients suffering from apparent rheumatoid arthritis may manifest several of the features of disseminated lupus erythematosus is still undecided. Neither is there at present any reliable means of determining whether a number of patients, in reality suffering from disseminated lupus, may run a chronic and relatively benign course simulating rheumatoid arthritis. Kievits et al. or reported a positive L.E. cell test in 17% of 488 patients suffering from "rheumatoid arthritis," and in this group there was a higher frequency of respiratory complications, splenomegaly, anemia, abnormal urinary sediment, false-positive tests for syphilis, high erythrocyte sedimentation rate and failure to respond to gold therapy. As no information was given regarding the Rose-Waaler test, it is possible that at least some of these patients actually had lupus erythematosus. Recently Heaton of has shown that a majority of

patients with Sjögren's syndrome have a positive L.E. cell test, and classic rheumatoid arthritis is also considered to be an integral feature of Sjögren's syndrome. Goslings,⁶² in studying rheumatoid subjects with pericarditis, found that some had a positive L.E. cell test and clinical evidence suggestive of disseminated lupus, but that others had neither. Present clinical and serologic means of investigation do not seem to be sufficient to clarify the questions of diagnosis and prognosis in these "borderline" cases. As far as our series of patients is concerned, all the evidence suggests that they were suffering from classic rheumatoid arthritis.

It is apparent that pleural effusion complicating rheumatoid arthritis occurs predominantly in men. 27, 32 The reasons for this are not clear. It is unlikely that previous or coexistent respiratory disease plays any part as a localizing factor. Of our nine patients with pleural effusion, only two had previous chest complaints; case 4 had mild recurrent bronchitis, and case 5 had had three attacks of pleurisy. Several other patients in the total of 180 had suffered from severe chronic bronchitis, with or without asthma, yet showed no evidence of pleural complications. Nor can occupational factors necessarily be held responsible for the pleural localization of the lesions. It is possible that previous exposure to coal dust conditioned the pulmonary lesions in cases 8, 9 and 10, who had all been underground mineworkers. This is more probable in case 8 who, in addition to bilateral recurrent pleural effusion, had radiologic and histologic evidence of the changes described in Caplan's syndrome. However, the occurrence of pleural effusion in patients with Caplan's syndrome has not been recorded, and the nodules in this patient were not absolutely typical in that they were not densely packed or layered with anthracotic pigment. Of the remaining male patients with pleural effusion alone, only one (case 7) had been an underground mineworker, and none of the others had been engaged in dusty occupations.

Of the 43 other male rheumatoid patients in the total series, four were underground mineworkers. Their chest radiographs showed respectively (1) no lesion, (2) no lesion, (3) early pneumoconiosis, and (4) a small area of collapse and bronchiectasis. There is thus no striking relationship between occupation and the development of pleural complications in our series, although such a possibility cannot be completely discounted.

It is possible that pleurisy with effusion represents an integral male feature of the rheumatoid process. Although the sex ratio of rheumatoid arthritis is usually two or three females to one male (in our series, approximately $2\frac{1}{2}$:1), the sex incidence of complications does not necessarily follow the same pattern. Thus keratoconjunctivitis sicca was shown to occur in a ratio of $6\frac{1}{2}$:1 (females: males) in a series of 210 rheumatoid subjects in which the overall sex ratio was 2.7:1.83

It is also clear from our series that pleural effusion may be a prodromal or inaugural event in the course of the rheumatoid process. This was definitely so in cases 1, 2, 3, 4 and 5, and probably so in case 7. In cases 8 and

9, in whom there were also parenchymatous lung lesions, the effusions did not develop until the arthritis had been present for two and one-half and two years, respectively. In the female patient (case 6), the pleural effusions developed 11 years after the onset of the arthritis. It is known that other extra-articular manifestations of rheumatoid disease (e.g., tendon lesions ⁶⁴ and ocular lesions ⁶⁵) may precede the development of arthritis. Parenchymatous pulmonary lesions may also anticipate the appearance of rheumatoid arthritis, Caplan's nodules having been recognized on radiographs several years before the development of joint lesions. ³⁴ It is important for the clinician to recognize the occurrence of a pleural effusion as a prodromal or inaugural event in rheumatoid arthritis, especially in middle aged males. The arthritic component may not be severe, and is apt to be overlooked in the investigation of a possibly serious chest condition.

The relatively frequent occurrence of pleurisy in our rheumatoid patients is in keeping with the high incidence of pleural fibrosis reported in several autopsy series.8,9,49,50 There was no evidence in our patients to suggest that pleurisy was associated with any of the other systemic complications of rheumatoid arthritis, or that the complication of pleural effusion necessarily carried a serious prognosis with respect to the arthritis. In fact, when we take the group as a whole, the outcome as judged by the functional capacity and disease activity has been good. This is in keeping with the finding that patients developing an acute type of rheumatoid arthritis necessitating hospital treatment usually fare very well.66 Of the eight male patients with pleural effusion, four are fully employed in their usual occupation, and one is fit for work but unemployed; one has worked continuously for seven years but is now suffering an exacerbation; the two patients with parenchymatous lung changes have only mild residual arthritis, but are prevented from working by their respiratory symptoms. The female patient (case 6) is only moderately incapacitated by her arthritis.

Of the seven patients with pleural effusion alone, resolution of the effusion occurred within a few months in six, after repeated thoracenteses. The seventh (case 4) developed a residual encysted effusion which is symptomless and has remained unaltered during the last 21 months. Only one patient (case 2) was given oral prednisone for his severe arthritis, although the effusion was already subsiding and continued to final resolution during the following few weeks.

In the patient with the diffuse fibrotic lung lesions (case 9), the effusion recurred repeatedly for about one year, then became encysted, although the pulmonary fibrosis has increased. The patient with nodular lung lesions (case 8) has had bilateral recurrent pleural effusions, but that on the right cleared up following corticectomy. He still requires thoracentesis of the left pleural sac about once yearly, due to slow recurrence of the effusion, but the nodular lesions have remained substantially unchanged for over five years. The patient with "honeycomb lung" has not required any treatment for his

pulmonary condition, which has remained unaltered during the last two years. Oral steroid therapy has been tried for this condition, without success.²⁸

In our patients, therefore, treatment of the pleural and pulmonary complications of rheumatoid arthritis has depended upon repeated thoracentesis. Thoracotomy and corticectomy were performed in one patient.

SUMMARY

One hundred eighty patients (52 males and 128 females) with rheumatoid arthritis seen during a period of two years were investigated for possible pleural and pulmonary lesions. Nine were found to have or to have had a pleural effusion for which no cause could be found other than rheumatoid disease. Eight of these patients were males. One further patient had radiologic evidence of a "honeycomb lung." The case histories of these 10 patients are presented.

The nine patients with pleural effusion have been under observation for periods ranging from 14 to 100 months (average, 48 months), and no evidence has developed of any other disease process that could have been responsible for the effusion. The importance of excluding other connective tissue disorders, tuberculosis and malignant disease is discussed.

Two of these patients (both males) also had coincident parenchymatous lung lesions; in one they were nodular, and in the other, diffuse and fibrotic. In both, the pleural and pulmonary lesions developed some time after the onset of the arthritis.

The other six male patients with pleural effusion had no evident lesions of the underlying lung. In all, the appearance of the effusion was accompanied by an acute febrile respiratory illness related to the onset of the arthritis. A review of the relevant literature has confirmed the view that pleural effusion complicating rheumatoid arthritis occurs predominantly in men. The only female patient with this complication in our series developed effusions several years after the onset of her arthritis.

It is concluded that pleural effusion occurs not infrequently in the course of rheumatoid arthritis, predominantly in men. It may be associated with parenchymatous pulmonary disease, but more commonly occurs as an isolated finding, and then is often an inaugural event in the disease. Rheumatoid arthritis merits a place in the differential diagnosis of pleural effusion, especially when this occurs in middle aged men and is associated with recent or developing joint symptoms.

ACKNOWLEDGMENTS

We wish to thank Dr. C. N. Armstrong, Dr. D. Ashby, Professor R. C. Browne and Mr. G. A. Mason for access to case notes of patients at some time under their care. We are also indebted to Dr. P. O. Leggatt for his advice and for undertaking the pleural biopsies, to Dr. I. Rannie for the histologic reports, and to Dr. S. Whately Davidson and his colleagues in the Department of Radiology. We are also grateful to Mrs. J. Dobson and Miss S. Jones for secretarial assistance.

SUMMARIO IN INTERLINGUA

Arthritis rheumatoide es considerate in nostre dies como un morbo generalisate capace a afficer, a parte le articulationes, varie histos e organos, incluse le pulmones e le pleuras. Le alterationes pleural pote esser nodular o diffuse, e effusion pleural ha essite reportate tanto como un constatation isolate in le presentia de morbo rheumatoide como etiam accompaniante un subjacente lesion pulmonar parenchymatose. Il existe reportos de lesiones nodular in le pulmones de patientes con arthritis rheumatoide, e tal lesiones ha etiam essite recognoscite como aspecto de pneumoconiosis rheumatoide o syndrome de Caplan. Il etiam occurre diffuse lesiones pulmonar. Istos prende le forma de un pneumonitis fibrosante interstitial, simile al syndrome describite per Hamman e Rich. Altere reportate formas de affection pulmonar in le processo rheumatoide es "pulmon faveolate" e arteritis pulmonar.

Cento octanta patientes, 52 masculos e 128 femininas, vidite con arthritis rheumatoide in le curso de un periodo de duo annos esseva investigate con respecto al presentia possibile de lesiones pleural e pulmonar. Esseva trovate que novem habeva o habeva habite un effusion pleural pro le qual nulle causa altere que arthritis rheumatoide poteva esser trovate. Octo de iste novem patientes esseva masculos. Un decime patiente exhibiva le apparentia radiologic de un "pulmon faveolate." Le historias clinic de iste 10 patientes es presentate.

Le novem patientes con effusion pleural ha essite sub observation durante periodos de inter 14 e 100 menses (con un duration medie de 48 menses), e un effortio special esseva facite pro excluder tuberculose pulmonar, carcinoma bronchogene, e systemic lupus erythematose.

Ha devenite manifeste nulle signo de un altere processo pathologic que poterea haber essite responsabile pro le effusion. Duo de iste patientes—ambes mascule—habeva coincidente lesiones pulmonar parenchymatose. In un caso, istos esseva nodular; in le altere, diffuse e fibrotic. In ambes le lesiones pleural e pulmonar se disveloppava un certe tempore post le declaration del arthritis.

Le altere sex patientes mascule con effusion pleural habeva nulle evidente lesion in le pulmon subjacente. In omnes le declaration del effusion esseva accompaniate de un acute febrile morbo respiratori que esseva relationate al declaration del arthritis. Un revista del pertinente litteratura ha confirmate le opinion que effusion pleural como complication de arthritis rheumatoide occurre predominantemente in masculos. Le unic feminina con iste complication in nostre serie disveloppava effusiones plure annos post le declaration de su arthritis.

Arthritis rheumatoide merita un placia in le diagnose differential de effusion pleural, specialmente quando isto occurre in homines de medie etate e quando illo es associate con recente o currente symptomas articular.

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SOME OBSERVATIONS ON THE TREATMENT OF POSTIRRADIATION HEMATOPOIETIC DE-PRESSION IN MAN BY THE INFUSION OF STORED AUTOGENOUS BONE MARROW * †

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THIS paper includes and extends the material presented at the meeting of the College a year ago.1 Since that time, we and others have had further experience with attempts to transplant donor bone marrow. Nothing in this experience causes us to alter the opinion we expressed a year ago, that donation of bone marrow in man has met with no more than transitory success, lasting up to a few weeks at best. Multiple blood group compatibility provides no guarantee of donor tissue compatibility. It is not at present possible to assure that immune mechanisms of the human recipient will not result in rejection of the donated tissue. Suppression of immune responsiveness by x-radiation in man may not occur at dosages below those which severely damage many tissues. Furthermore, if transplantation should be successfully performed, homologous disease is likely to ensue. This situation, which has been studied in experimental animals, appears to be due to the production of antibodies by the donated leukocytes against the recipient's tissues.

To avoid these difficulties, we have introduced the repopulation of suppressed marrow with stored autologous marrow, i.e., the patient's own marrow. The marrow is collected from the ilia with siliconized apparatus containing 2 to 5 units of heparin per milliliter of marrow, diluted with an equal volume of 30% glycerol in tissue culture medium, § and frozen by cooling at the rate of 1° C. per minute to -79° C. prior to institution of the bone marrow suppressive therapy. We shall first review the experience which has led us to conclude that this procedure is feasible and results in rapid

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‡ Phases of this work were submitted in a thesis in partial fulfillment of requirements for the Master of Arts degree at Long Beach State College.

§ TC 199—Difco Laboratories, Detroit, Michigan; Hank's or Osgood's solution.

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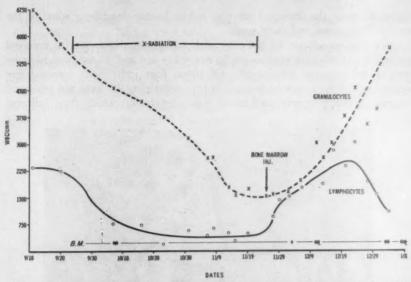


Fig. 1. Case 1. Granulocyte and lymphocyte response to extensive irradiation (400 KV, 3 mm. copper filtration, half value layer 4.2 mm. copper, 400 r in air daily, 5 days per week to ports varying in size from 10 by 10 cm. to 15 by 20 cm.; total, approximately 2,000 r (tissue) to the node-bearing areas. Nine ports were used, including inguinal, opposing abdominal, opposing mediastinal, and supra-clavicular) and bone marrow injection, Sept., 1957–Jan., 1958. Bone marrow response (BM) is indicated on scale +++ normal, + severely hypoplastic, ++++ hyperplastic.

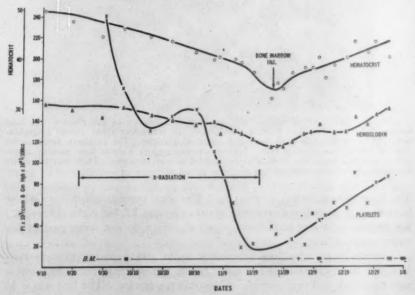


Fig. 2. Case 1. Hematocrit, hemoglobin and platelet counts during above period.

repopulation of the damaged marrow before briefly describing some of the studies in progress and their goals.

We can report on 14 patients with malignant diseases who received extensive radiotherapy six months to two years ago and whose bone marrow was stored prior to irradiation. Of these, four individuals received five reinfusions of their own bone marrow; the remaining 10 were not reinfused because of the relatively mild blood count depression which they suffered.



Fig. 3. Case 1. Bone marrow one week after completion of radiotherapy and bone marrow injection. All bone marrow photographs are low power views (initial magnification, 100×) of formalin-fixed, sectioned aspirated particles. The pertinent detail is the ratio of fat to bone marrow cells. Lighter staining regions without bone marrow architecture represent blood clot, in some areas crowded with erythrocytes. These may be readily distinguished from the bone marrow particles.

The latter group served as controls. The total number of patients whose bone marrow was stored up to six months ago was 22, but eight of these did not receive extensive radiotherapy and therefore do not form part of the study reported here.

Limitation of time does not permit us to give a review of each case. We have therefore selected two patients into whom the stored bone marrow was reinfused, and two controls to illustrate the results. The first was a 36

year old white male with testicular teratoma and pulmonary metastases. Over a two-month period (figure 1), following bone marrow storage in September, 1957, he received approximately 2,000 r (tissue) to the nodebearing areas of the torso. As shown in figure 1, the radiotherapy induced marked leukopenia, with only 1,500 granulocytes remaining. Following the intravenous infusion of his own preserved bone marrow containing approximately 400 million viable nucleated cells which had been diluted with hypertonic glucose and saline,2 the granulocyte count rose to 6,000 in 40

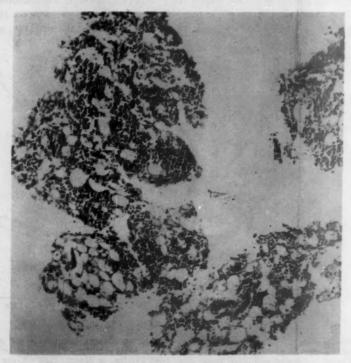


Fig. 4. Case 1. Bone marrow one month after figure 3.

days. The recovery of the bone marrow (to be described in greater detail later) is indicated on the line marked "B.M." The 3 - at the beginning of irradiation designates normocellular marrow; the 1+ following irradiation indicates severely hypoplastic marrow, which was followed by rapid recovery to essentially normal, indicated by 21/2 +, within two weeks after bone marrow infusion, and subsequent hyperplasia, indicated by the $3\frac{1}{2}$ + after six weeks. Figure 2 shows the fall in platelet count to 15,000 per cubic millimeter, and in hematocrit and hemoglobin to approximately 65% of the original, induced by the radiotherapy. The red cell parameters returned to normal 40 days following infusion of the bone marrow, while the platelet count rose to 90,000. The bone marrow revealed severe aplasia upon the completion of radiotherapy, and was still markedly depressed seven days following the bone marrow infusion (figure 3). The high proportion of fat to cellular elements is notable. This marrow already contains numerous islands which are predominantly erythropoietic, with increased mitotic activity. One week after that, a repeat bone marrow aspiration (figure 4) showed a marked progressive increase in both myeloid and erythroid activity. Six weeks after the completion of his radiotherapy and bone marrow infusion, the patient became paraplegic due to an extradural mass in the lower thoracic spine. At this time the marrow, which

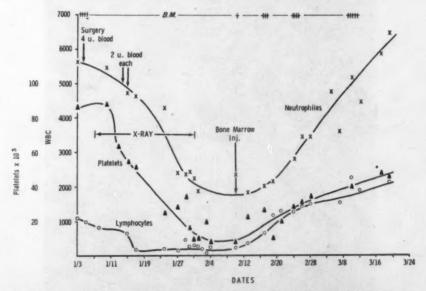


Fig. 5. Case 1. Granulocyte, lymphocyte, platelet and bone marrow (BM) response to second course of x-radiation to five 10 by 20 cm. ports obliquely directed to the lumbodorsal spine (estimated additional tissue dose, 2,000 r), Jan. to March, 1958. X-ray factors were essentially the same as for figure 1.

had become hyperplastic, was again collected and preserved. He then received 2,000 r (tissue dose) to the lumbodorsal spine through multiple ports over a two-week period. The effect of the repeat therapy is shown in figure 5. Because of the bone marrow suppression, reflected by the granulocyte count of 1,800 and platelet count of only 10,000, associated with bleeding, his stored marrow, containing approximately 600 million nucleated cells, was reinfused. As indicated in the figure, the granulocyte count rose to over 6,000 and the platelet count to 50,000 in five weeks. The recovery from lymphopenia, which may be an index of lymphoid regeneration and

recovery of immunologic mechanisms, was equally rapid. Again the marrow recovered from the postirradiation depression shown in figure 6 to the normocellular state one week later (figure 7), and to the hypercellular state one week thereafter (figure 8).

The second patient is a 40 year old man with renal carcinoma with pulmonary metastases. Following the collection of bone marrow (figure 9), he received 500 r in air to each half of the torso on successive days, thus

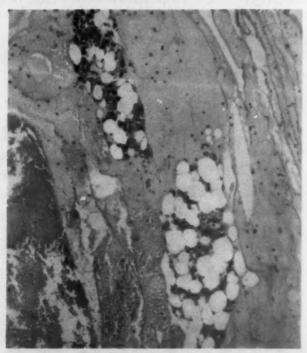


Fig. 6. Case 1. Bone marrow (sternal) one day after second bone marrow infusion (2/10/58).

receiving a "total body" dose of 500 r in air, with only minimal regression of the renal mass. Immediately after the radiotherapy he received approximately 2½ billion nucleated marrow cells intravenously. Radiation-induced leukopenia (1,800/cu. mm.) and thrombocytopenia (40,000/cu. mm.) ensued. Beginning at the third week after the bone marrow infusion, rapid recovery occurred. The leukocyte and platelet counts rose to the pretreatment levels by the fifth week, and to supranormal values thereafter. Bone marrow aspiration (figure 10), performed one week following the completion of radiotherapy and infusion of the bone marrow, revealed hypoplasia. The marrow was still moderately hypocellular one and two

weeks later, but with marked erythroplasia and reticulum cell hyperplasia. Thereafter, the marrow increased rapidly in cellularity, returning to normal within four weeks after the bone marrow infusion, and becoming markedly hypercellular by the fifth week after infusion (figure 11). Unfortunately, despite the success of the bone marrow implantations, the tumors proved to be radioresistant, and the patients ultimately succumbed to the metastatic disease.

In summary, regeneration and hyperplasia of severely radiation-depressed marrow occurred in one and a half to four weeks following the infusion of

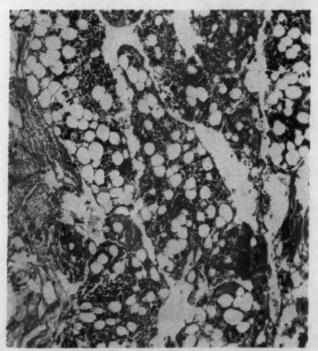


Fig. 7. Case 1. Bone marrow one week after figure 6.

stored autologous bone marrow. Of the other two patients, one responded similarly, and the other died 10 days after irradiation, with evidence of bone marrow regeneration.¹

The 10 control patients were all treated for seminoma with approximately 2,000 r (tissue) to the node-bearing areas of the torso over a period of from seven to 12 weeks following the bone marrow storages. Since in these patients the platelet count did not fall below 60,000 per cubic millimeter, or the white blood cell count below 1,600, their stored marrows were not reinfused. The data on a typical patient are shown in figure 12. Whereas

nine months following his first course of radiotherapy, which included only the lower half of the torso, this 64 year old man had recovered from the induced leukopenia, his bone marrow was still moderately hypoplastic. Following the demonstration of metastatic supraclavicular nodes, further radiotherapy was administered in May and June, 1958, consisting of 2,000 r (tissue) to the mediastinum and supraclavicular fossae. Gradual but incomplete recovery of the peripheral count ensued spontaneously, reaching approximately pretreatment levels after seven months; but bone marrow aspirates three months after completion of the radiotherapy (figure 13)

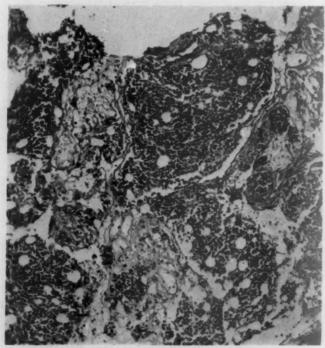


Fig. 8. Case 1. Bone marrow one week after figure 7.

were still markedly hypoplastic, and after 10 months the marrow was still moderately depressed, as contrasted with the hyperplasia of the marrow of the infused patients within one and a half to four weeks.

A second control patient (case 4) is a 32 year old man with seminoma without known metastases. As shown in figure 14, his peripheral blood counts recovered spontaneously: the leukocytes returned to normal three months following radiation, and the platelets somewhat later. However, his bone marrow (figure 15) was still severely hypoplastic eight months after completion of therapy.

Of the remaining eight control patients observed six months or longer following bone marrow depression by extensive radiotherapy, none has to date shown spontaneous recovery of the marrow to normocellularity. Three, followed more than one year, now have marrows which we rate as 1+ to 2+ (severe to moderate hypoplasia). The peripheral blood counts returned to the low-normal range in from two weeks to seven months, despite persistence of bone marrow depression.

The bone marrow cells probably remain viable indefinitely at -79° C. Marrow thawed immediately after freezing and after storing for 18 months

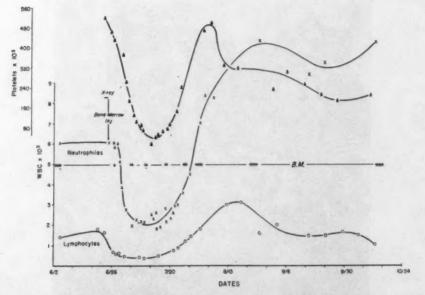


Fig. 9. Case 2. Platelet, neutrophil and lymphocyte response to 500 r (air) to each of two 30 by 30 cm. anterior ports (upper and lower one-half torso) on two successive days (250 KV, 5 mm. Cu filter, HVL 1.7 mm. Cu, 75 cm. TSD), followed by bone marrow injection. Bone marrow response as in figure 1.

was found to show over 90% of the cells to be viable * on both occasions. The cells, diluted by the Sloviter method, appeared to be morphologically intact, and were motile.

The minimal number of autologous cells required to achieve marrow repopulation in man has not been determined. The lowest number we have used successfully is 400 million nucleated cells. We are now investigating this problem in our control subjects whose marrow continues to be hypoplastic. By infusing small samples of their stored marrow, we hope to be able to determine the number required to produce rapid recovery.

We have recently discontinued diluting the marrow for reinfusion ac-

POSTIRRADIATION HEMATOPOIETIC DEPRESSION

cording to the Sloviter method, and are simply diluting it with one-half volume of 35% glucose. The preserved marrow is quickly thawed in a 37° C. water bath. As soon as it becomes liquid, while still cold, it is diluted with one-half volume of cold 35% glucose.* As soon as convenient thereafter, it is infused intravenously at a moderately rapid rate. We routinely collect bone marrow from all patients with normal marrow who are to receive extensive radiotherapy or bone marrow suppressive chemotherapy for malignancies and lymphomata.

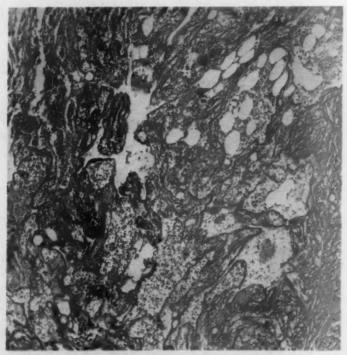


Fig. 10. Case 2. Bone marrow one week after completion of radiotherapy.

With this safeguard, we can administer more intensive radiotherapy to larger areas in a shorter time, and we have been more inclined to complete planned courses despite leukopenia and thrombocytopenia. During the last two years we have also been preserving marrow from patients with acute and chronic leukemia during induced remissions so as to have available morphologically normal autologous marrow for reinfusion following intensive therapy during subsequent relapses. A program for intensive

^{*}Clumping is greatly reduced by this procedure as compared to the previously used dilution method.² Thawing at 0° C. appears to be even more satisfactory.

therapy of patients with Hodgkin's disease following bone marrow storage is planned. This program consists of treating the spleen and all node-bearing areas with approximately 2,400 r tissue dose in divided doses, in the hope that recurrences may be prevented by obliteration of the sites. This possibility is encouraged by the experience that isolated node areas treated with cancerocidal doses are rarely the sites of recurrence of Hodgkin's disease. We have not yet reinfused the stored marrows into patients with leukemia or Hodgkin's disease.

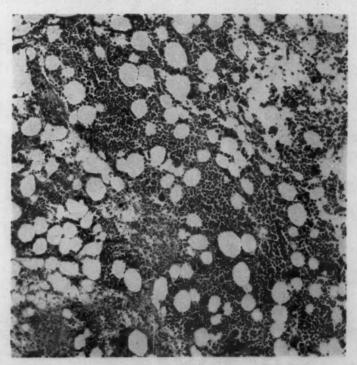


Fig. 11. Case 2. Bone marrow five weeks after completion of radiotherapy.

It is our opinion that the preservation and subsequent reinfusion of autologous bone marrow is a safe and effective adjunct to the therapy of malignant disease with bone marrow suppressive agents, including radiation and chemical agents. The banking of marrow of individuals whose occupations entail hazard of excessive radiation would therefore appear to be a reasonable precaution.

The patients have generally tolerated the intensive and extensive radiotherapy well. In no case have reactions been troublesome or required interruption of therapy. The experience with control subjects who did not

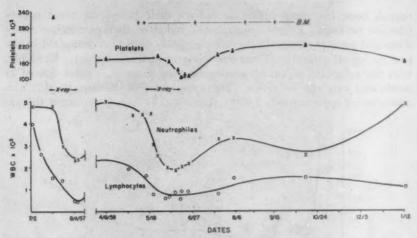


Fig. 12. Case 3. Control. July, 1957-January, 1959. The x-ray factors were the same as for case 1. The first course of radiotherapy, 7/19/57 to 8/15/57, was to five ports varying from 10 by 15 to 15 by 15 cm., including right iliac, umbilical, lumbar, epigastric and low dorsal areas, 400 r daily, total, approximately 2,000 r (tissue) to the node-bearing regions. The second period of radiotherapy, 5/16/58 to 6/16/58, was to 4 ports, 10 by 15 cm. each, including supraclavicular and opposing mediastinal ports, 400 r daily, 2,400 r (tissue) total.

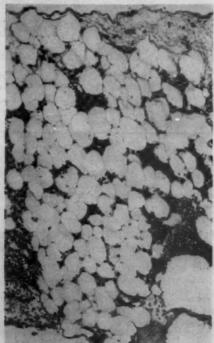


Fig. 13. Case 3. Bone marrow three months after completion of radiotherapy.

require bone marrow infusion to correct their peripheral blood counts (despite persistent marrow hypoplasia) indicates that permissible x-ray doses and rates of administration have probably been underestimated in the past (a logical precaution, since overdosage was irremediable). Certainly, with the safeguard of stored autologous bone marrow, greater dosage at accelerated rate can be given. The experiences of Newton et al.,6 who administered approximately 3,000 r (tissue) in 14 days to the entire thorax,

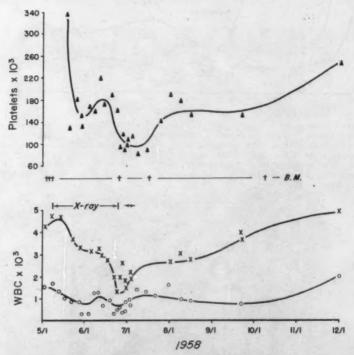


Fig. 14. Case 4. Control. May to December, 1958. X-ray factors as for figure 1. Radiotherapy, 5/7/58 to 7/3/58, was to 8 ports, varying from 10 by 10 (supraclavicular) to 20 by 20 (mediastinal) cm., including same ports and rate as figure 1, 2,200 r (tissue) total to the node-bearing regions.

and of McGovern et al.⁷ who administered single doses of approximately 500 r total body, appear to confirm our observations on the efficacy of autologous bone marrow infusion.

APPENDIX

Recommended Procedure for the Collection and Preservation of Bone Marrow: Under local anesthesia and morphine sulfate sedation, a siliconized * #16 or larger

^{*}Silicone Z-4141 (Dow-Corning) 1:4000, dried 24 hours at room temperature before autoclaving.

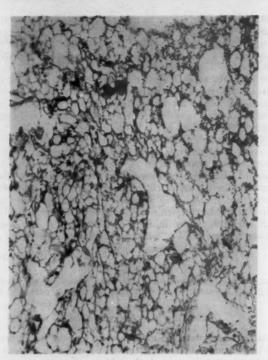


Fig. 15. Case 4. Bone marrow six months after completion of radiotherapy. Aspirate in October 1958, 16 months after radiotherapy, showed same hypocellularity.

spinal needle * is inserted into the posterior iliac crest. A siliconized 50 c.c. syringe containing 2 ml. heparin (100 units/ml. in isotonic saline) is attached, and approximately 60 ml. of bone marrow are aspirated. Aspiration is interrupted approximately every 10 ml. and the syringe disconnected to permit mixing with the heparin by repeated inversion. During this procedure the stylus, swabbed with heparin solution, is replaced in the needle to prevent clotting. Upon each following connection of the syringe to the needle, the position of the needle point in the marrow cavity is changed. The marrow is distributed in 5 ml. aliquots into siliconized screw-capped test tubes. The procedure is repeated in the opposite ilium. A small representative sample of the marrow is used for total cell count, differential count, desoxyribonuclease activity 4 and viability determination by a modification of the Schrek method 3 (0.2 ml. bone marrow suspension diluted with 0.1 ml. 331/2% dextrose in water and 0.3 ml. 2% trypan blue in Ringer's solution). Pending the collection of adequate information on the number of marrow cells required for repopulation of the marrow, we seek to collect 2.5 to 3 × 10° nucleated marrow elements. This goal is generally exceeded by the collection of 120 ml. of marrow as described, and rarely is it necessary to repeat the procedure. The procedure is well tolerated by ambulatory patients.

To each 5 ml. of marrow, 5 ml. of 30% glycerol in tissue culture medium (TC199,

^{*} Becton, Dickinson & Co., #461 LNRC, 16 gauge. Through the courtesy of this company we have obtained a similar needle, 13 gauge, with two holes bored in the last one-half inch of the three and one-half inch cannula. We recommend the latter needle.

Hank's or Osgood's) are added. The marrow is then promptly frozen at the rate of 1° C, per minute to -29° C, and then at approximately 2 to 3° C, per minute to - 79° C.5 in a special freezing apparatus.* The test tubes containing frozen marrow are sealed in a plastic bag and stored in a dry ice chest at -79° C, until required for reinfusion.

The marrow is thawed at 0° C. (cold room or ice bath). With a #13 siliconized needle and siliconized syringe, the marrow is removed from the test tubes and transferred to a plastic bag.† Slowly, with continuous mixing, 1/2 volume of cold -331/2 to 35% glucose in water is added. A sample is taken for cell count, differential count and viability determination.

The bulk of the marrow, diluted with one-half volume of glucose as described, is infused intravenously at the rate of 50 to 60 drops per minute through a #17 siliconized needle, without filter. When all the marrow has run in, the plastic bag and filter are rinsed by the infusion of several hundred milliliters of Ringer's solution. With this technic, unlike the result obtained when dilution is performed according to the Sloviter method, clumping is avoided. The small particles that do appear readily pass through the needle, with only occasional manipulation. We have encountered no ill effects from the infusion of marrow. In one patient, transitory gross hemoglobinuria occurred, but without symptoms or untoward signs.

ACKNOWLEDGMENT

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SUMMARIO IN INTERLINGUA

Pro le tractamento de aplasia del medulla ossee inducite in humanos per mesuras therapeutic, nos ha proponite-con le objectivo de evitar le difficultates e complicationes resultante de graffos de medulla ossee ab altere humanos qui functiona como donatores -que on pote practicar le re-infusion de autologe medulla ossee colligite ante le tractamento e preservate durante le intervallo per congelation in glycerol. Dece-quatro patientes ha essite sub observation satis prolongatemente pro permitter un evalutation. Inter istes, quatro esseva subjicite a cinque aspirationes de medulla ossee, sequite per radiotherapia e re-infusion del medulla. In le altere 10 casos, le re-infusion non esseva effectuate proque le patientes habeva suffrite minus sever lesiones del medulla ossee. Istes esseva tenite sub observation como subjectos de controlo e examinate serialmente per numerationes sanguinee e aspirationes de medulla.

Le hyperplasia inducite intra alicun septimanas in le gruppo recipiente le reinfusiones, in contrasto con le prolongate hypoplasia del medulla ossee in le gruppo de controlo, indica que le manovra es de valor. Per consequente nos expande le programma del infusion de medulla autologe per preservar medulla ab (1) patientes leucemic in remission pro un subsequente re-infusion eventual si recidivas require un intense suppression de medulla ossee per droga o irradiation e (2) patientes de morbo de Hodgkin in qui nos propone instituer un tractamento initial con doses cancerocidal de radios X applicate a omne areas nodifere sin reguardo a si o non illos es evidentemente afficite. In plus nos propone usar le mesme programma in le caso de personas in qui il existe le risco occupational del contraction de lesiones del medulla ossee.

sachusetts.

^{*} Canalco Slow-Freeze Unit. Canal Industrial Corporation, Bethesda, Maryland. Immediate freezing without incubation with glycerol causes less protection of the erythrocytes (i.e., greater hemolysis in thawing), but provides maximal nucleated cell survival. †Fenwal Transfer Pak, No. TA-1. Fenwal Laboratories, Inc., Framingham, Mas-

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THE CURRENT STATUS OF CHEMOTHERAPY OF SYSTEMIC FUNGAL DISEASE *

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THIRTY years ago this June, Fleming 1 first reported the antibacterial action of cultures of Penicillium, thus in one sense inaugurating the Antibiotic Era. During this period many antibiotics have been developed and used successfully in treating bacterial diseases. However, only two mycoses. actinomycosis and nocardiosis, have responded to any of these antibacterial drugs. In the four years since a symposium on the therapy of systemic fungal infections,2 a number of new and promising antifungal drugs have been developed, and one of these, amphotericin, has been given clinical trials in a large number of patients. These considerations have prompted this present review of the therapy of systemic mycoses, based for the most part on our own experience with patients treated in the Clinical Center, National Institutes of Health.

Bed-rest, or other limitation of activity; proper diet, usually high-calorie, high-protein; and supportive medical and nursing care are advisable for all systemic mycoses. Drainage or, when possible, excision of the lesion at the proper time is often beneficial. Chemotherapy supplements these measures.

ACTINOMYCOSIS

For many years, iodides and roentgen irradiation have been recommended forms of treatment for actinomycosis. Since the work of Florey. penicillin has been used in an increasing number of cases, and, more recently, isolated case reports have described cures with chlortetracycline, sulfadiazine, streptomycin and chloramphenicol. Cases collected from the literature 8 disclose that the administration of penicillin in large amounts for prolonged periods of time was successful in the treatment of 36 of 42 patients with thoracic actinomycosis. In our own experience, in one patient the administration intravenously of 10,000,000 units a day for eight weeks was effective.

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Nocardiosis

For nocardiosis, sulfadiazine in amounts necessary to achieve a serum level of from 9 to 12 mg.% is the treatment of choice. In our opinion, however, it needs to be supplemented by an antibiotic, preferably penicillin. Of the four patients we have seen with this infection, three have cleared the organism from the site involved and have made satisfactory recoveries after the following treatments: sulfadiazine and phenoxymethyl penicillin (V), 600,000 units every four hours orally for two months; sulfadiazine and phenoxymethyl penicillin (V), 800,000 units every four hours orally for three months; sulfadiazine, streptomycin, 1 gm. daily intramuscularly for six weeks, and procaine penicillin G, 600,000 units every six hours intramuscularly for two months.

ASPERGILLOSIS

Aspergillus fumigatus and occasionally other species are encountered in patients with pulmonary infiltration or pneumonitis and, in addition, isolated examples of mycetoma, paranasal sinusitis, dacrocystitis, meningitis, endocarditis and osteomyelitis have been associated with infection by this fungus. The recent reports 4,5 of six additional fatal cases of aspergillosis emphasize the occasionally serious nature of this disease. Iodides in the form of potassium or sodium salts, and vaccine therapy, have been recommended for such systemic infections. That iodides alone may not always be strikingly effective has been suggested by our own experience.4 In two patients with cavitary pulmonary disease, the administration of potassium iodide in gradually increasing dosage to a maximum of 30 gm, a day continued for two and one-half weeks to one patient, and 24 gm. for three and one-half weeks to the other, was associated with clearing of Aspergillus niger from sputum or abscess drainage material. It is worth emphasizing, however, that this improvement in two patients with A. niger infection treated with iodides might not be duplicated in other patients infected with A. fumigatus, which more often invades tissue and disseminates. In our two patients, evidence of tissue invasion of A. niger was not present. Furthermore, treatment with these large doses of iodides was associated with disturbance in mental status in one patient, and with abnormalities in serum electrolytes in both. These and other serious manifestations of iodism should thus be watched for. Iodides in smaller doses have been standard treatment also in systemic sporotrichosis, geotrichosis and penicilliosis.6

MUCORMYCOSIS

There is little experience in the therapy of mucormycosis, because these infections for the most part have been recognized only at autopsy. They have occurred in debilitated patients, especially those with diabetes, cancer and leukemia. In a nonfatal case, it has been suggested 6 that the control

of the underlying disease was the most important factor in treating the infection. Experimental work in animals supports this belief, at least in the instance of diabetes.⁷ Four additional patients apparently have been cured, however, by the surgical removal of the focus of infection. In one of these cases no preceding complicating disease had been present, although the patient developed glycosuria one year after surgery.⁸

HISTOPLASMOSIS

A. Sulfonamides: Although Christie has recently of recommended sulfonamides, reports on their use in the treatment of histoplasmosis have been contradictory. Experimental work by Louria and Feder in our laboratory showed that in vitro sulfadiazine had a marked fungistatic effect in a concentration of 10 mg.%. In usually fatal mouse infections, a sulfadiazine serum level of from 1 to 17 mg.% was found to exert a marked protective effect when treatment was begun on the day of infection. Less but still significant protection was achieved when treatment was delayed up to 10 days after infection. A marked decrease in the positivity of cultures in a small group of animals killed five and one-half weeks after termination of therapy was observed. In our experience with human disease, however, sulfadiazine was inadequate treatment in four cases of disseminated, fatal histoplasmosis.

B. MRD-112: Despite early optimistic reports ¹¹, ¹² of the action of MRD-112 (biethyl aminoethyl fencholate) in fungal infections, subsequent studies with this drug have for the great part been discouraging. It was found to be ineffective in the treatment of experimental histoplasmosis in mice. In one patient with a fatal infection we used it without benefit in dosage that for 40 days was approximately 10 times that previously used in other cases. We have abandoned the use of this drug.

C. Ascosin: Ascosin is an antibiotic produced by Streptomyces canescus. It was first reported ¹⁸ to be effective in experimental histoplasmosis. In these studies, however, the therapeutic dose approached the toxic level. We have used the drug in only one patient, immediately prior to his death, in dosage of 0.015 mg./Kg., without detectable change. We know of no other studies of ascosin in human beings.

D. Endomycin: The manufacturer of endomycin reported that it was relatively nontoxic for mice, and that in vitro histoplasma, and also blastomyces, coccidioides and cryptococcus, were inhibited in concentrations of 1.25 to 2.5 µg./ml. In vivo experiments in mice did not show it to be effective, however, against experimental histoplasmosis or cryptococcosis, and this failure was corroborated by our experience in five patients with these two diseases. Two succumbed to their disease, and the remaining patients were not benefited.

E. Amphotericin B.: A more promising drug, amphotericin B, an antibiotic prepared from a species of streptomyces, is effective in vitro against some strains of histoplasma, cryptococcus, blastomyces, coccidioides and candida. It is poorly absorbed from the gastrointestinal tract of man, and one clinical trial ¹⁴ of oral therapy failed in 13 patients with culturally proved mycoses. Although some patients noted subjective improvement, only two of 13 improved objectively, and in only one case did cultures become negative. Since these earlier studies, we have used this drug by the intravenous route in seven patients with histoplasmosis. The forms of amphotericin used, the methods of drug administration and the clinical studies performed have been previously reported. ¹⁵ The desired dose of intravenous preparation was added to 250 or 500 ml. of 5% solution of glucose and given by infusion during a period of from three to six hours. After a test dose of from 1 to 5 mg., the desired final dosage was reached by daily increments of 5 to 10 mg. With a few exceptions, patients received daily treatment. Maximal therapeutic dosage was 100 mg. daily (2.0 mg./Kg.), and the

TABLE 1
Histoplasmosis: Treatment with Amphotericin Intravenously

| No. | Pt. | Age | Color Sex | Duration of Illness Prior to Treatment (Mos.) | Sites of Positive Cultures | Total Dose (Mg.) | Maximal Daily Dose (Mg.) | Cultural Status | Outcome and Follow-up Period |
|-----|-------|-----|--------------|---|--|------------------------|-----------------------------------|--------------------|---------------------------------|
| 2 | н. н. | 57 | WM | 25 | Blood, urine, bone marrow, ascitic fluid | 5570 | 60 | Negative | Apparent recovery, 2 years |
| 3 | G, G. | 1/2 | NM | 1 | Blood, urine, spu- tum, bone marrow, pleural fluid | 30 | 10 | Positive | Dead |
| 15 | J. K. | 35 | WM | 1 | Bone marrow, spu- tum | 885 | 100 | Negative | Apparent recov- ery, 1 year |
| 16 | W. T. | 38 | NM | 2 | Bone marrow | 1260 | 40 | Negative | Apparent recov- ery, 1 year |
| 26 | J. B. | 72 | WM | 1 | Blood, bone mar- row, gastric wash- ings | 2181 | 50 | Negative | Apparent recovery, 6 months |
| 27 | О. В. | 74 | WM | 11 | Blood, bone mar- row, urine, oral ulcer | 460 | 50 | Positive | Dead |
| 28 | М. Р. | 62 | WM | 6 | Blood, bone mar- row, cerebrospinal fluid | Over 2000 | 70 | Negative | Improved. On treatment |

range of dosage given daily to all other patients was from 0.6 to 1.5 mg./Kg. The results of treatment are shown in table 1. Four of seven patients with histoplasmosis observed for 1/2-2 years following treatment have made apparent recoveries from their disease. Two patients died, and one is currently on therapy. Most patients received large amounts of the drug, although one, who recovered, received less than 1 gm. Seabury ¹⁶ has also reported improvement in three of four cases treated.

CRYPTOCOCCOSIS

In 1956 Littman and Zimmerman, in a monograph on cryptococcosis, ¹⁷ critically reviewed reports of the use of over 60 agents in the nonsurgical therapy of this disease. They concluded at that time that, in disseminated or cerebral disease, the most reasonable medical therapy was cyclohexamide

Table 2
Cryptococcosis: Treatment with Amphotericin Intravenously

| No. | Pt. | Age | Color Sex | Duration of Illness Prior to Treatment (Mos.) | Sites of Positive Cultures | Total Dose (Mg.) | Maximal Daily Dose (Mg.) | Cultural Status | Outcome and Follow-up Period |
|-----|-------|-----|--------------|---|-------------------------------|------------------------|-----------------------------------|--------------------|-----------------------------------|
| 5 | D. J. | 43 | WF | 54 | Cerebrospinal fluid | 1750 | 30 | Negative | Improved, 1 year |
| 6 | D. K. | 36 | WF | 15 | Cerebrospinal fluid | 223 | 20 | Unknown | Unchanged |
| 7 | W. G. | 50 | WM | 25 | Cerebrospinal fluid | 2989 | 40 | Negative | Apparent recov- ery, 21 months |
| 8 | J. N. | 48 | WM | 64 | Cerebrospinal fluid, urine | 4227 | 40 | Positive | Unchanged |
| 9 | H. S. | 37 | WF | 10 | Cerebrospinal fluid, urine | 638 | 20 | Negative | Apparent recov- ery, 20 months |
| 17 | J. N. | 77 | NM | 77 | Cerebrospinal fluid | 621 | 50 | Positive | Dead |
| 30 | C. M. | 25 | WM | 2 | Cerebrospinal fluid | 3000 | 50 | Positive | Improved, 2 months |
| 31 | C. P. | 61 | WM | 18 | Cerebrospinal fluid | 2-3000 | 80 | Positive | Unchanged |

(Acti-dione) or 2-hydroxystilbamidine. However, neither of these drugs had been shown to be effective in experimental infection of animals, and only six patients were reported to have benefited. Recently, two drugs have shown promise in experimental infections in animals, and one of these, amphotericin, has undergone clinical trial in man.

A. Silver: Several silver salts have been shown to prolong, by a factor of 2–5, the survival times of mice with experimental cryptococcosis. Silver salicylate gave the best protection, but other silver preparations, including silver proteinate, were nearly as effective. To our knowledge, only one patient, in 1923, was treated with a silver preparation, given in colloidal form, intrathecally, for three days, without apparent change in clinical status. To

B. Amphotericin: Our experience with the intravenous use of amphotericin in man is shown in table 2. Two of eight patients with cryptococcal meningitis have apparently recovered, whereas two other patients were improved, three were unchanged, and one has died. When intrathecal and intravenous therapies were combined (table 3), three additional patients improved and one died. These findings are in general agreement with

TABLE 3
Cryptococcosis: Treatment with Amphotericin Intravenously and Intrathecally

| No. | Pt. | Age | Color Sex | Previous Therapy | Intrathecal Dose (Mg.) | Intravenous Dose (Mg.) | Cultural Status | Outcome and Follow-up Period |
|-----|-------|-----|--------------|------------------------------|------------------------------|----------------------------|--------------------|---------------------------------|
| 8 | J. N. | 48 | WM | Unsuccessful I.V. therapy | 0.5 b.i.w., 22 injections | 20 q.d., 811 total | Negative | Improved, 10 months |
| 29 | J. D. | 21 | WM | None | 1.0 q.o.d., 27 injections | 50-100 q.d., 4755 total | Negative | Improved, 9 months |
| 30 | C. M. | 25 | WM | Unsuccessful L.V. therapy | 0.5 t.i.w., 29 injections | 50 q.o.d., 800 total | Positive | Dead |
| 31 | C. P. | 61 | WM | Unsuccessful I.V. therapy | 0.5 t.l.w. | 50 q.o.d. | Negative | Improved. On therapy |

those of other physicians. Rubin ²⁰ observed improvement in six and apparent recovery in two of 10 treated patients. Seabury ¹⁶ reported improvement in five of seven patients, and Newcomer ²¹ in three of five patients.

BLASTOMYCOSIS

A. 2-Hydroxystilbamidine: The treatment of blastomycosis with 2-hydroxystilbamidine has been termed "reasonably satisfactory," ² and, for the most part, the case reports and summaries of treated cases have agreed with this statement. However, Harrell ²² in one publication and Cherniss ²³ in another stated that, in their series, treatment with 2-hydroxystilbamidine was successful in only one third of their patients. The one patient with blastomycosis that we treated with 2-hydroxystilbamidine was not benefited.

TABLE 4
Blastomycosis: Treatment with Amphotericin Intravenously

| No. | Pt. | Age | Color Sex | Illness | Duration of Illness Prior to Treatment (Mos.) | Sites of Positive Cultures | Total Dose (Mg.) | Maximal Daily Dose (Mg.) | Cultural Status | Outcome and Follow-up Period |
|-----|-------|-----|--------------|---------------------------------|---|--|------------------------|-----------------------------------|--------------------|------------------------------------|
| 11 | D. R. | 74 | NF | Chronic | 36 | Sputum | 110 | 15 | Positive | Unchanged |
| 12 | C. A. | 45 | WM | Osteomyelitis and cellulitis | 12 | Bone marrow, urine, sinus tract drain- | 5185 | 45 | Negative | Apparent recovery, 15 months |
| 18 | R. S. | 44 | NM | Pneumonia and cellulitis | 2 | Sputum, sinus tract drain- | 2516 | 40 | Negative | Apparent recovery, 1 year* |
| 19 | W. O. | 20 | NM | Osteomyelitis and cellulitis | 4 | Sputum, sinus tract drain- age | 2298 | 30 | Positive | Relapse, 8 months |
| 32 | E. B. | 51 | WM | Skin granuloma | 80 | Skin | 740 | 35 | Negative | Apparent recovery, 6 months |

^{*} Developed pulmonary tuberculosis eight months after treatment.

B. Amphotericin: Our experience with amphotericin B in blastomycosis is shown in table 4. Three patients with blastomycosis have apparently recovered from their illness and have remained well for from six months to 15 months following therapy. One patient relapsed eight months after treatment, and one additional patient was not affected by a probably inadequate dosage of drug. All four patients treated by Seabury 16 improved, as did one reported by Newcomer. 21

Coccidioidomycosis

Chemotherapy of disseminated coccidioidomycosis in man was termed "universally disappointing" ²⁴ in 1955. In the period since 1955, our own experience with amphotericin would not suggest a change in this statement.

A. Amphotericin (table 5): In all of our four patients with coccidioidomycosis, the cultures have remained positive. Newcomer, 21 however, has

Table 5
Coccidioidomycosis: Treatment with Amphotericin Intravenously

| No. | Pt. | Age | Color Sex | Illness | Duration of Illness Prior to Treatment (Mos.) | Sites of Positive Cultures | Total Dose (Mg.) | Maximal Daily (Mg.) | Cultural Status | Outcome and Follow up Period |
|-----|-------|-----|--------------|---|---|---|------------------------|---------------------------|--------------------|------------------------------------|
| 14 | A. J. | 81 | WF | Chronic pulmo- nary with bron- cho-pleural fis- tula | 38 | Sputum | 2600 | 40 | Positive | Unchanged |
| 20 | L. D. | 29 | NM | Chronic pulmo- nary and syno- vitis | 17 | Sputum, spinal fluid | 1660 | 60 | Positive | Unchanged |
| 21 | J. F. | 25 | NF | Chronic pulmo- nary synovitis and cellulitis | 25 | Subcutane- ous ab- scesses | 7300 | 100 q.o.d. | Positive | Improved, 1 month |
| 33 | P. G. | 23 | NM | Chronic pulmo- nary and cere- bellar abscess | 43 | Cerebro- spinal fluid, cerebellar tissue | 800 | 80 | Positive | Dead |

reported improvement after amphotericin treatment in six of nine patients with disseminated coccidioidomycosis involving bone, skin and lung. Two of five patients with meningitis were also benefited. Littman ²⁵ noted a beneficial effect in four treated cases of coccidioidomycosis. The one patient treated by Seabury ¹⁶ improved temporarily, but died while on therapy. Necropsy revealed many large abscesses containing viable coccidioides.

CANDIDIASIS

A. Mycostatin: Mycostatin, an antibiotic derived from a culture of Streptomyces noursei, is effective when taken by mouth for oral or enteric candidiasis, or when applied locally to skin infections due to candida. The drug is not absorbed, however, from the gastrointestinal tract, and is ineffective by this route in systemic fungal infections. The intravenous preparation which we used was extremely toxic, and is no longer available for study.

B. Amphotericin: Our experience with amphotericin in candida infections is shown in table 6. Three patients with candida endocarditis and one

TABLE 6
Candidiasis: Treatment with Amphotericin Intravenously

| No. | Pt. | Age | Color Sex | Illness | Duration of Illness Prior to Treatment (Mos.) | Sites of Positive Cultures | Total Dose (Mg.) | Maximal Daily Dose (Mg.) | Outcome and Follow-up Period |
|-----|-------|-----|--------------|---|---|----------------------------------|------------------------|-----------------------------------|------------------------------------|
| 22 | R. A. | 31 | WM | C. albicans | 2 | Cerebrospinal | 2136 | 40 | Dead |
| 23 | G. V. | 46 | WM | meningitis C. parapsilosis endocarditis | 11 | fluid Blood | 831 | 50 | Dead |
| 24 | A. W. | 40 | WM | C. albicans endocarditis | 1 | Blood | 2370 | 60 | Dead |
| 25 | A. S. | 57 | WM | C. albicans septicemia | 1 | Blood | 110 | 40 | Apparent recovery, 10 months |
| 34 | M.S. | 39 | WF | C. guilliermondi endocarditis | 1 | Blood | 140 | 50 | Dead |

TABLE 7
Summary: Treatment with Amphotericin Intravenously and Intrathecally

| Disease | Apparent Recovery | Improved | Unchanged | Dead | Total |
|-----------------------------------|----------------------|----------|-----------|------|-------|
| Histoplasmosis | 4 | 1 | 0 | 2 | 7 |
| Cryptococcosis | 2 | 4 | 1 | 2 | 9 |
| Blastomycosis | 3 | 1* | 1 | - 0 | 5 |
| Coccidioidomycosis | 0 | 1 | 2 | 1 | 4 |
| Coccidioidomycosis Candidiasis | 1 | 0 | 0 | 4 | 5 |
| | 10 | 7 | 4 | 9 | 30 |

^{*} Relapse.

patient with candida meningitis have died despite amphotericin therapy. One patient with Candida albicans septicemia complicating a pyelonephritis has made an apparent recovery.

A summary of amphotericin treatment of five mycoses is shown in table 7. The toxic reactions to amphotericin are given in table 8. These have commonly been fever, chills, nausea, and rise in the blood urea nitrogen. In 22 of 30 cases with blood urea nitrogen rise, dosage was reduced or

TABLE 8
Reactions to Amphotericin B Intravenously

| 1. Shaking chills | 26/30 |
|----------------------------------|-------|
| 2. Fever | 26/30 |
| 3. Nausea | 19/30 |
| 4. Vomiting | 13/30 |
| 5. B.U.N. rise | 22/30 |
| a) causing a change in treatment | 19/22 |

Other: anorexia, headache, vertigo, slight drop in blood pressure, anemia.

therapy interrupted for a few days, but in no instance did treatment have to be stopped. In all instances the toxic effects were reversible at the end of therapy.

SUMMARY

In actinomycotic infections, penicillin is still the most effective chemotherapy. Sulfadiazine in combination with an antibiotic is recommended in cases of nocardiosis. Iodides and vaccine therapy have been the major therapeutic measures recommended in cases of aspergillosis. Iodides are also standard treatment for sporotrichosis, geotrichosis and penicilliosis. There is little experience in the therapy of mucormycosis, and success has been achieved in a few cases by the surgical removal of the focus of infection, or by the control of an underlying disease, e.g., diabetes. In the treatment of histoplasmosis and blastomycosis, amphotericin appears to be effective. Amphotericin, similarly, seems to be the best drug thus far for cryptococcosis. Amphotericin is least effective in systemic coccidioidomycosis and candidiasis, but worthy of use in the absence of other, effective chemotherapy.

SUMMARIO IN INTERLINGUA

In le curso del 30 annos depost le prime reporto de Fleming del action antibacterial de culturas de Penicillium, multe antibioticos ha essite disveloppate e usate a bon successo in le tractamento de morbos bacterial. In recente annos un numero de nove e promittente drogas antifungal ha essite disveloppate, e un de illos ha essite usate in essayos clinic in grande numeros de patientes. Como resultato de iste studios, e particularmente de nostre experientias con patientes tractate al Centro Clinic del Institutos National de Sanitate, nos has summarisate le stato currente del therapia de systemic morbos fungal. In infectiones actinomycotic, penicillina remane le plus efficace agente chimotherapeutic. Sulfadiazina in combination con un antibiotico es recommendate in casos de nocardiosis. Ioduros e therapia vaccinal ha essite le principal mesuras recommendate in casos de aspergillosis. Ioduros es etiam le tractamento standard pro geotrichosis e penicilliosis. Experientia in le therapia de mucormycosis es restringite; in un certe numero de casos le ablation chirurgic del foco de infection ha resultate in bon successos o etiam le stabilisation de un morbo subjacente, como per exemplo diabete. In le tractamento de histoplasmosis a blastomycosis, amphotericina pare esser efficace. Il pare similemente que amphotericina es (usque nunc) le melior droga pro cryptococcosis. Amphotericina es le minus efficace in systemic coccidioidomycosis e candidiasis, sed mesmo in casos de iste morbos illo merita esser usate in le absentia de un altere plus efficace chimotherapia.

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DRUG-INDUCED HEPATIC INJURY *

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Drug-Induced hepatic injury poses many problems. Establishment of a causal relation between a hepatic disease, usually with jaundice and preceding intake of a drug, is often difficult. This question arises with increasing frequency in view of the continuing expansion of the use of drugs. The instances of jaundice appearing in the last few years following administration of "tranquilizers" and "energizers" are cases in point. In the following the attempt is made: (1) to trace the difficulties in the recognition of the causal relation between drug administration and liver damage; (2) to describe the possible approaches to the solution of the problem; (3) to discuss the main hepatic alterations which occur following drug therapy, illustrating each with recently observed examples; and (4) to survey the possible ways for prevention of the injury. Discussion of the problem is given preference over an attempt at an exhaustive survey of the literature on drug-induced injuries, which are covered by a series of recent reviews.1,2,3

DIFFICULTIES IN ESTABLISHING THE ETIOLOGY OF DRUG-INDUCED HEPATIC INTURY

1. The liver participates in many systemic reactions as part of a variety of diseases; for instance, in infections involving organs other than the liver, and in disorders of the gastrointestinal tract, the liver shows alteration of its parenchymal cells, including focal necrosis and mobilization of Kupffer cells, as well as portal inflammatory reactions. These changes have been collectively designated as nonspecific reactive hepatitis.4 They may be associated with varying degrees of abnormalities in the results of hepatic tests, and with such clinical manifestations as enlargement and tenderness of the organ. Even more impressive are the hepatic alterations resulting from circulatory disturbances like cardiac failure or shock in an organ which is notoriously sensitive to oxygen deficiency as well as to pressure effects. Conspicuous centrolobular necrosis as found in autopsy specimens may simply be produced by agonal processes, and not be related at all to the

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actual disease before the terminal period. Even in biopsy specimens, such changes may be a reflection of circulatory disturbance and not of a specific drug effect. They are sometimes associated with severe alteration in the laboratory findings—for instance, steep elevation of the transaminase activity of the serum. Laboratory and histologic changes may thus not be an effect of the drug, but rather of the underlying disease for which the therapy had been instituted.

2. Hepatitis and jaundice can result from serum hepatitis virus incidental to the parenteral therapy directed toward the disease, rather than from the express toxicity of the drug administered. Most types of jaundice following antisyphilitic therapy were originally attributed to the drugs, 8, 9 and only after much groping were many recognized to be viral hepatitis. 10, 11

3. The liver may be the site of a disease, e.g., viral hepatitis or extrahepatic biliary obstruction from stones or tumors which is entirely independent of the drug therapy. The latter may have been instituted to combat early symptoms of the underlying disease. This is particularly the case in extrahepatic biliary obstruction.

4. The history as to the administration of the drug is sometimes unreliable because of either deliberate concealment or lack of observation. In a series of autopsy observations in which the liver morphologically exhibited a picture strongly suggestive of toxic injury, a drug was implicated only in the minority of instances.¹² Toxicologic demonstration of many of the offending agents is notoriously difficult.

5. The liver responds to injury with a limited number of reactions, which makes it difficult to establish the hepatic effect of one drug.

6. The evaluation of the morphologic changes is hindered by the lack of standardized criteria and nomenclature in liver disease. It is difficult to interpret the histologic lesions reported in the literature, apparently more so than in any other organ.

Approaches to the Establishment of the Etiology of Hepatic Drug Injury

1. Statistical evaluation: The obvious indication of a causal relation between drug intake and hepatic injury is the occurrence of liver disease in high incidence following the intake of a drug. This is particularly the case with poisons—for example, those of an industrial nature ⁸—and occurs in drug therapy in instances in which the vehicle used in the therapy appears to be poisonous. In most reported cases of hepatic injury following therapy with a drug, only a relatively small number develop liver disease, and the statistical data are at best ambiguous.

2. Functional investigation: If, following the administration of test doses to human subjects or experimental animals, results of the so-called liver function tests become regularly abnormal, and particularly if they return to normal after cessation of the therapy, the drug is probably hepatotoxic.

However, few tests measure well defined functions of the liver.¹⁴ Most of the hepatic tests—as, for example, the serum protein reactions—only indirectly indicate altered hepatic activities,¹³ and are not necessarily influenced

by drug-induced injuries.

- 3. Challenge: If re-administration of small amounts of a drug which has been implicated with jaundice produces it again, or at least clinical or laboratory manifestations of hepatic injury, the causative role of the drug appears to be confirmed. This phenomenon, thought to be an indication of hypersensitivity, does not occur regularly. For instance, readministration of chlorpromazine is sometimes well tolerated in otherwise substantiated intoxications.²⁷ Hepatic hypersensitivity disease is, at best, poorly understood.
- 4. Pathologic study: Because of the limited number of morphologic reactions of which the liver is capable, changes found cannot be expected to characterize one drug. However, groups of drugs do produce defined hepatic reactions like cholestasis or centrolobular necrosis. Even this statement is further qualified by the different types of alteration which have been reported to follow the administration of the same drug, particularly the sulfonamides. 15, 16, 17, 18, 19, 20, 21, 22, 23 Also, cinchophen has been reported by some to produce mainly fatty metamorphosis,24 and by others, massive necrosis.25 It is possible that, just as viral hepatitis produces hepatocellular necroses of various types as well as cholestasis,4 drugs may have multiple effects on the liver. However, in view of the difficulties listed, the role of incidental factors is always moot. The most revealing procedure is the performance of liver biopsy in a series of patients before and after drug therapy. This somewhat elaborate procedure can clarify the questions of incidence and nature of the injury.26

5. Animal experimentation: The causal relation sought is strongly supported if administration of the drug to experimental animals produces a hepatic lesion similar to that observed in the patient. The literature is contradictory even on this point. For example, various reports of animal hepatotoxicity of cinchophen have not withstood careful scrutiny. Dogs seem to be more sensitive than rats or mice to hepatotoxic effects of various

drugs.30

6. Pathogenesis: Some hepatotoxic drugs have a well known biochemical effect—for instance, amine oxidase inhibition in the case of iproniazid, or the inhibition of Krebs' cycle enzymes by carbon tetrachloride. Involvement of basic, primarily enzymatic, processes in the liver suggests an etiologic relation.

SURVEY OF DRUG REACTIONS

The approaches described can be utilized in a listing of entities with particular emphasis on those recently encountered. Morphology has been used as a guidepost to list five groups of reactions.

1. Zonal hepatocellular alterations without inflammatory reaction: A variety of drugs produce zonal changes of the liver cells, either necrosis or fatty metamorphosis, or both. The typical example is carbon tetrachloride, which causes necrosis and disappearance of liver cells in the centrolobular zone, with conspicuous fatty metamorphosis and sometimes also hydropic cell swelling in the intermediate zone, whereas the peripheral liver cells either appear normal or regenerate to compensate for the damage elsewhere in the lobule ^{38, 34} (figure 1). The portal tracts are usually involved to a surprisingly small degree. Sometimes the liver cells of the entire lobule are involved, as in the fatty metamorphosis of chloroform intoxication. ³⁵ The lesion is produced by drugs which actually should be considered as poisons, and, indeed, the picture resembles that caused by many known poisons, such

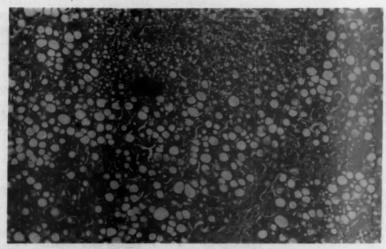


Fig. 1. Autopsy specimen of acute carbon tetrachloride intoxication, showing necrosis of the cells in the centrolobular zone (arrow), fatty metamorphosis in the intermediate zone, and preservation of a few cells in the lobular periphery (H & E ×63).

as phosphorus ³⁶ or mushroom poison. ^{37, 38, 39} The poison may affect the kidney to a great degree, and frequently it is difficult during life and even after autopsy to decide as to whether hepatic or renal failure was of greater clinical significance.

As a rule, a statistical relation is obvious, and the extent of the lesion is dependent upon the dose; virtually everybody exposed to a given amount shows characteristic lesions. Alcoholism or malnutrition commonly accentuates this.¹ The lesion can be reproduced in various species of experimental animals at will, and carbon tetrachloride intoxication, for example, is a favorite tool in production of experimental hepatic injury. Similarly, functional changes in experimental animals and in man are readily observed,

especially following industrial exposure. Pathogenetically, some of the substances have been shown to interfere with defined hepatic enzyme systems, e.g., carbon tetrachloride poisons mitochondrial enzymes.³² The metabolic character of the injury is reflected in the zonal distribution of the lesion; all liver cells in a given zone, presumably similar metabolically, are involved to an equal degree.¹² This apparently best understood type of drug injury is at present, in view of its predictable character, the least important in clinical medicine.

2. Intrahepatic cholestasis: A group of drugs without common chemical structural characteristics produce, in a small number of patients exposed to them, jaundice which resembles extrahepatic biliary obstruction in its clinical, functional and even histologic manifestations 40 (table 1). These

TABLE 1 Cholestatic Drugs

| Generic Name | Trade Name | Associated with Inflammation | Incidence | References |
|------------------------|------------------------|------------------------------|----------------|---|
| Arsphenamine | | + | Few cases | 65, 66 |
| Carbarsone | | 7 | Isolated cases | 67 |
| Methyltestosterone | | 0 | Few cases | 79, 86, 81, 82, 83 |
| Norethandrolone | Nilevar | 0 | Less than 1% | 84, 85, 26 |
| Chlorpromazine | Thorazine Largactil | + | 1-2% | 41, 42, 43, 44, 45, 46, 47, 48, 55, 56, |
| | Megaphen | | | 60, 61, 64, 139, |
| Prochlorperazine | Compazine | 3 | Isolated cases | 49 |
| Ectylurea | Nostyn | 7 | Isolated cases | 50 |
| Mepazine | Pacatal | . 3 | Isolated cases | 51 |
| p-aminosalicylic acid | | + | Few cases | 68, 69 |
| p-aminobenzyl caffeine | 100000 | 0 | Isolated cases | 77 |
| Chlorthiazide | Diuril | 7 | Isolated cases | 78 |
| Sulfanilamide | | + | Few cases | 15 |
| Sulfadiazine | | 0 | Isolated cases | 153 |
| Thiouracil | 1000,000 | + | Few cases | 72, 73, 74 |
| Methimazole | Tapazole | 0 | Few cases | 75, 76 |
| Chlorpropamide | Diabenese | + | Isolated cases | 141 |
| Dinitrophenol? | - Labertebe | 1 2 | Few cases | 122 |

drugs include tranquilizers, particularly chlorpromazine, with which clinicians have had the greatest experience. A different incidence is stated by various observers, the best estimate available being between 1 and 2%. Related substances, such as prochlorperazine, mepazine, ectylurea and promazine, apparently produce cholestasis in very rare instances, whereas no examples are known to us following intake of trimeprazine and trifluoperazine.

The patients appear to be less sick than the degree of jaundice would indicate. Itching has occasionally been reported. The serum protein reactions are normal in many instances, but may become abnormal after long duration of jaundice. Serum transaminase activity is elevated in most instances, but seldom above 200 units with the standard colorimetric

method. 58, 54 Serum activity of alkaline phosphatase is also increased, as are total serum cholesterol and the sedimentation rate.55 Circulating eosinophils may be elevated. Bromsulfalein retention is common. 56 The duration of the disease varies from a few weeks to many months, 57, 58 and transition into a chronic stage has been rare, but in one instance even xanthomatous biliary cirrhosis has been reported. 50 The mortality rate is very low; 60, 61 in our own autopsy material,62 one case was seen while five additional cases observed in other institutions were studied on a consultation basis. Some of the fatal cases died after exploratory operation for the possibility of an extrahepatic biliary obstruction. The cause of death seems to have been hepatic failure in all cases, in view of some recorded signs of coma with an elevated serum ammonia level, at least in one case.

Histologically, three manifestations are present. 48, 62, 68, 64 The most conspicuous is bile stasis, predominantly in the center of the lobule zone, reflected in bile plugs in the canaliculi, bile-pigmented protein coagulates in liver cells, bile-pigmented granules in Kupffer cells, and extracellular accumulation of bile (figure 2). Some surrounding liver cells show rarefaction of their cytoplasm (feathery degeneration). Where liver cells disappeared in the centrolobular zone, mononuclear cells accumulated. The second feature is infiltration of the edematous portal tracts by mononuclear cells with a varying admixture of eosinophils. Also, ductular cells proliferate within the portal tract and in the peripheral zone of the parenchyma, and usually are surrounded by the same type of exudate cells. The borders of the portal tracts eventually become indistinct, and the limiting plate is disorganized. The third feature is focal necrosis of the liver cells, with replacement by mononuclear cells. Of these features, only the first is considered to be significant, whereas the others are transient. In the fatal cases the bile stasis, sometimes associated with 'terminal hypoxemic fatty metamorphosis or central necrosis, is very severe, whereas the inflammatory reaction has virtually disappeared, suggesting that cholestasis rather than inflammation was responsible for the clinical manifestations and the hepatic failure 62 (figure 3). The actual mechanism of hepatic failure under these circumstances is unknown, in view of the morphologic preservation of the liver cells in the greater part of the lobule.

Another example of a drug apparently producing both cholestasis and portal inflammatory reaction is arsphenamine, the description of which was historically the first reported cholestatic drug injury. 65 It occurs in only a very small group of those treated with arsenicals, and in only a small percentage of those developing jaundice after arsenical therapy, the vast majority being the result of syringe-transmitted hepatitis. Some of the cases of the arsenical injury, now only rarely observed, progressed to chronic biliary hepatitis with xanthomatosis, 66 but apparently even then recovery was the rule. The arsenical amebicide, carbarsone, apparently also produces

cholestasis.67

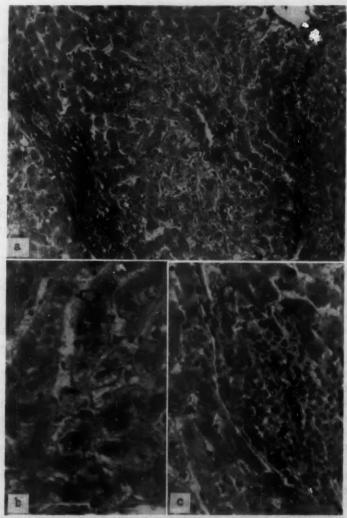


Fig. 2. Biopsy specimen of jaundiced patient who had received chlorpromazine. (a) Centrolobular bile stasis and portal inflammation (H & E \times 120). (b) Higher magnification of centrolobular zone, showing bile plugs in dilated bile canaliculi (arrow), and bile pigment in Kupffer cells and liver cells (H & E \times 400). (c) Portal tract infiltrated by mononuclear and segmented cells, as well as proliferation of ductular cells (arrow) (H & E \times 400).

Among other drugs producing cholestasis with portal inflammatory reaction should be listed chlorpropamide, of which a case recently came to our observation, and para-aminosalicylic acid, 88, 69, 70, 71 sulfadiazine, thiouracil, 72, 78, 74 methimazole, 75, 76 8-para-aminobenzyl caffeine, 77 and chlor-

thiazide.⁷⁸ No fatality occurred to our knowledge in the course of the cholestatic phase, and recovery apparently was always the rule. The situation is somewhat confused in the case of para-aminosalicylic acid, in which various types of hepatic injuries without cholestasis have been reported,^{70, 71} and which cannot so far be put into the scheme just presented.

Another group of drugs producing cholestatic injury is represented by methyltestosterone ⁷⁹⁻⁸² and its recently developed analog, norethandrolone, ^{26, 83-85} which is recommended for its protein anabolic effect. These drugs produce the same type of centrolobular cholestasis, which may sometimes be severe. However, portal inflammation is not found even transiently. ²⁶ The incidence of cholestasis is below 1% with the doses usually used.

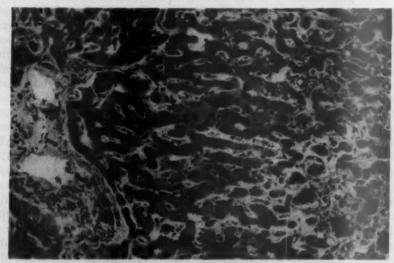


Fig. 3. Autopsy specimen of patient who died during jaundice which followed the administration of chlorpromazine. Centrolobular bile stasis is seen, with minimal infiltration of the portal tract. The liver cells are intact in the greater part of the lobule (H & E $\times 120$).

With all cholestatic drugs, the relation to the dose of the drug is at best hazy; single doses of chlorpromazine are reported to have produced jaundice. 89, 87 In the case of methyltestosterone, it is said never to occur if not more than 25 mg. per day are given. Little indication can be found that pre-existing liver diseases, such as cirrhosis or biliary tract disease, predispose to hepatic injury; an exception is the observation of aggravation of jaundice in cases of primary biliary cirrhosis who received testosterone analogs for relief of pruritus. 85

Hepatic tests in patients on various cholestatic drugs who do not develop jaundice have not rendered uniform results.^{89, 90, 91, 92} Furthermore, jaun-

dice may disappear with continued administration of the drug. 93, 94 Even without jaundice, serum alkaline phosphatase activity may occasionally increase, and it has been stated that this subsides with interruption of therapy. 83 The only alteration frequently seen in nonjaundiced patients upon administration of cholestatic drugs is Bromsulfalein retention, occurring after administration of norethandrolone. 85, 85

Attempts to reproduce the cholestatic lesion in normal animals have failed. While chlorpromazine does not seem to aggravate most experimental hepatic injuries, 90 it does accentuate ethionine intoxication in rats. 95 It has also been claimed to be beneficial in other types of experimental

intoxications.96

The pathogenesis of the cholestatic lesion is indeed difficult to clarify. As the old question of intrahepatic cholestasis or "cholangiolitis," which has challenged the ingenuity of clinicians and pathologists for many years, it presents the thorniest problem in the differential diagnosis of jaundice. Previous consideration and deductions have led to the hypothesis that the basic alteration is that of the membranes of the liver cells forming the bile canaliculi.97 Clinical and functional alterations in intrahepatic bile stasis are best understood if a defect of these membranes is postulated. Recent electron microscopic investigations confirmed this hypothesis, in that in druginduced intrahepatic cholestasis (which is the most readily available uncomplicated form of this condition), the bile canaliculi are characteristically altered. The microvilli of the canalicular lining in intrahepatic cholestasis are deformed in a way similar to that in extrahepatic biliary obstruction. In the latter condition, these changes are always associated with dilatation of the canaliculi, while in intrahepatic cholestasis this is not necessarily the case. Eventually, in both conditions, connections between bile canaliculi and projections of the intrahepatic tissue spaces develop, and may produce an added element of regurgitation. In other types of jaundice, such as the noncholestatic type of viral hepatitis, or in Dubin-Johnson disease, the microvilli are not altered. It thus appears that intrahepatic cholestasis is a primary disorder of the bile canaliculi which leads to the formation of an abnormal bile and is followed by an intrahepatic obstructive phenomenon, with regurgitation similar to extrahepatic obstruction. This explains the similarity in the clinical and laboratory manifestations between extrahepatic biliary obstruction and intrahepatic cholestasis.

The lack of correlation between the portal, frequently periductal and periductular inflammatory reaction and the degree of jaundice, at least in acute stages, excludes inflammation as a pathogenetic factor in cholestasis.²⁶ The eosinophilic character of the portal inflammation and the frequent skin manifestations suggest the hypersensitivity nature of the portal reaction. A similar infiltration characterizes other hepatic hypersensitivity reactions without jaundice.²⁶ Whether the lesion of intrahepatic cholestasis is hyperergic in nature is to date a matter of mere conjecture.

TABLE 2
Drugs Producing Viral Hepatitis-Like Picture

| Generic Name | Trade Name | Incidence/Mortality | rtality References | | |
|--|-----------------------------------|---|--|--|--|
| Iproniazid | Marsilid | Low/20% | 99, 100, 101, 102, 103, 104 | | |
| Cinchophen Zoxazolamine Sulfamethoxypyridazine | Atophan Flexin Kynex PZA | Low/50% Isolated cases Isolated cases 3%/10% | 24, 25, 28, 29, 100 107 23 142, 143 | | |

3. Hepatic necrosis with inflammatory reaction: Single cell necrosis with single cell regeneration progressing first to zonal and then to massive necrosis, throughout associated with conspicuous inflammatory reaction, characterizes typical viral hepatitis. Some drugs produce these morphologic manifestations as well as most of the clinical and laboratory features of viral hepatitis (table 2). At present, the example most frequently seen is the hepatic reaction following the administration of the amine oxidase inhibitor, iproniazid. ^{90, 100, 101, 102, 103, 104} Clinically, severe hepatocellular failure with all of its laboratory manifestations and deep jaundice is observed. Intrahepatic cholestasis is sometimes in the foreground, just as it is occasionally in viral hepatitis. ¹⁰⁵ The mortality rate has been high, averaging about 20% of those afflicted. In contrast, the incidence is very low and has

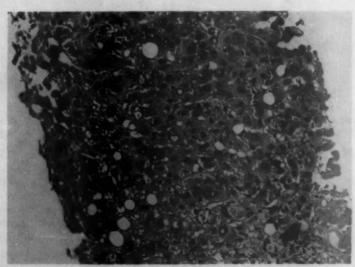


Fig. 4. Liver biopsy specimen of patient (of Dr. Henry Dolger) who had received chlorpropamide (Diabenese) for control of diabetes and developed jaundice. Centrolobular bile stasis is noted (curved arrow), portal inflammation (straight arrow), mild fatty metamorphosis and ballooning of liver cell nuclei because of glycogen deposition (H&E ×120).

been stated to be around 1:4000. Features not frequently seen in viral hepatitis include the usual absence of fever, the very deep jaundice, and a deceptive disparity between the severity of the morphologic changes and the less impressive clinical manifestations. No distinct relation to the dose of the drug and the duration of its administration could be established. Preëxisting liver disease does not seem to be a predisposing factor. Histologically, all stages are seen, from single cell necrosis associated with acidophilic bodies and accumulation of mononuclear cells replacing necrotic liver cells and infiltrating the portal tracts (figure 6), to massive necrosis ("acute yellow atrophy") with collapse of the framework (figure 7), to

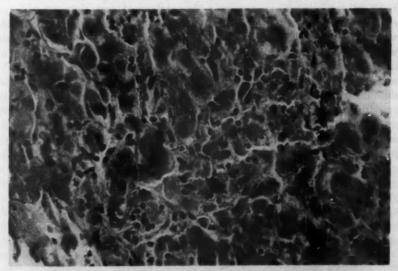


Fig. 5. Liver biopsy specimen from a patient who developed jaundice while receiving iproniazid (Marsilid). Diffuse hepatocellular degeneration is seen, with single cell necrosis and regeneration and interstitial infiltration by mononuclear cells. Straight arrow points to round liver cell with homogeneous acidophilic cytoplasm and pyknotic nucleus. Curved arrow points to bile cast (H & E ×240).

subacute atrophy with beginning nodular regeneration (early postnecrotic cirrhosis). One sees all of the features usually considered to be characteristic of viral hepatitis, such as lipofuscin accumulation, proliferation of ductules surrounded and infiltrated by mononuclear cells and segmented leukocytes, and phlebitis of the hepatic veins. While iproniazid-induced hepatic injury has been studied morphologically more thoroughly because of the availability of a considerable number of liver biopsy and autopsy specimens, other drugs undoubtedly produce the same picture. An example is cinchophen, according to the available literature; it is no longer widely used because of its hepatotoxic effect. 24, 25, 28, 29, 106 The incidence of hepatic in-

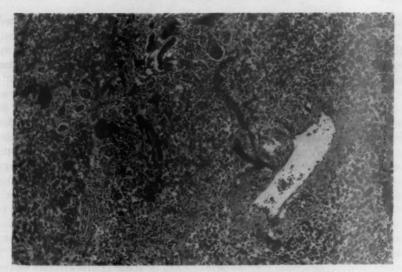


Fig. 6. Autopsy specimen from patient dying with jaundice associated with iproniazid therapy, showing diffuse hepatocellular necrosis with accumulation of scavenger cells and collapse of framework, proliferation of ductules on the periphery of the lobule (straight arrow), and infiltration of wall of hepatic vein tributary by inflammatory cells (curved arrow) (H&E ×63).

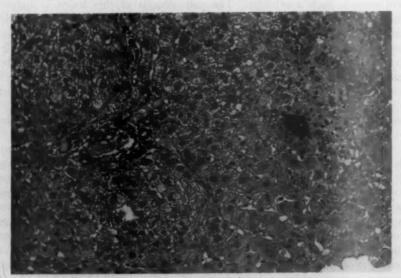


Fig. 7. Liver biopsy specimen from a patient (of Dr. Henry Dolger) who developed jaundice after metahexamide therapy for control of diabetes, exhibiting extensive centrolobular necrosis (arrow), moderate portal inflammation and few areas of focal necrosis (H&E ×120).

jury is low but the mortality rate is about 50%, again without an established relationship to the dose given.^{28, 29} The pathologic observations recorded, although variable, indicate a picture belonging to this group. Two autopsy specimens in our own material show acute massive necrotic hepatitis similar to that found in fulminant viral hepatitis.

Another drug with two fatal cases of acute hepatic necrosis recorded is zoxazolamine, 107 and an opportunity to study the specimens convinced us of the similarity of the morphologic manifestations. The same was concluded from a recently studied case of death following treatment with pyrazinamide.

Low incidence associated with high mortality is apparently characteristic of this group of drugs. No clear-cut evidence is known to us that the drugs listed, particularly iproniazid, produce alterations in the results of hepatic tests in nonjaundiced human subjects or in experimental animals. Experimental production of hepatic lesions in animals exposed to these drugs is controversial. It has been claimed for sulfamethoxypyridazine ⁸⁰ and for cinchophen, ²⁰ but the evidence is not convincing. Similarly, iproniazid has been stated not to produce lesions in experimental animals, although a recent abstract describes regular development of acute yellow atrophy of the liver after short-term administration of large doses of an amine oxidase inhibitor to dogs. ¹⁰⁸ This has not been the experience of another group. ¹⁰⁹

The recognition of the causal relation is particularly difficult in this group because of the similarity to viral hepatitis, and only a sufficient incidence will suggest such a relation. The pathogenesis of this lesion is indeed shrouded in mystery. The inability to produce the lesion in animals would raise the possibility of activation of preëxisting virus, for instance, of the serum hepatitis type by the drug. 103, 110 However, iproniazid does not aggravate mouse virus hepatitis. 111 If the experimental production of the lesion by various drugs should be confirmed, the conclusion has to be drawn that the morphologic picture previously considered to be characteristic for viral hepatitis may be produced by drugs of entirely different chemical constitutions. Whether this represents a common hyperergic reaction to the virus and to various drugs is a matter of conjecture.

4. Unclassified group: The literature is replete with reports about many drugs being associated with a variety of hepatic injuries which do not easily fit into a scheme (table 3). Many of the injuries are centrolobular or focal necrosis. Some are said to progress to massive necrosis, and then possibly they belong in the previously described group. 112, 113, 114 In some instances the cellular reaction and bile duct proliferation appear to be less conspicuous. 115 The same drugs—for instance, the sulfonamides 22, 116 or the anticonvulsants 117-121—are reported to produce different lesions, like central necrosis, focal necrosis or even granulomas. In many of the reported examples, morphologic substantiation is missing. 122, 123, 124, 125, 126, 127, 128 A characteristic of this group is the conspicuous involvement of other organs, particularly bone marrow changes, skin eruptions, interstitial myocarditis or

nephritis.^{118-118, 121} In some members of the group, the hepatic alteration may indeed be secondary to the involvement of the other organs. Changes produced by dinitrophenol,¹²⁹ gold salt therapy ^{180, 181} or drugs used in treating cancer ^{182, 188, 184, 188} probably are the result of a reproducible toxicity. In most other instances, isolated, often even single examples are reported suggesting hypersensitivity. Animal experiments, in most instances, have not reproduced the lesions, and the cases deserve further attention, particularly concerning the incidence of the lesion and for better classification. A case in point is a recently observed instance of mild jaundice following metahexamide which was associated with centrolobular as well as focal necrosis and accumulation of mononuclear cells (figure 7). However,

Table 3
Unclassified Group of Drugs Associated with Hepatic Injury

| Generic Name | Trade Name | Trade Name Incidence | | | |
|-----------------------|--|----------------------|-------------------------|--|--|
| Isoniazid | | Few cases | 112, 144, 145, 146, 152 | | |
| p-aminosalicylic acid | The state of the | Few cases | 70, 71, 147 | | |
| p-aminobenzoic acid | of the state of th | Isolated cases | 113 | | |
| Oxophenarsine | Mapharsen | 1:450 | 8, 9 | | |
| Diphenylhydantoin | Dilantin | Few cases | 119, 126 | | |
| Phenacemide | Phenurone | Few cases | 118, 120, 121, 148 | | |
| Trimethadione | Tridione | Few cases | 117 | | |
| Gold salts | | 1:400 | 130, 131 | | |
| Sulfanilamide | 11000 -00 | Few cases | 16, 17, 18 | | |
| Sulfadiazine | | Few cases | 19, 20, 21 | | |
| Chlortetracycline | Aureomycin | Few cases | 149, 150, 151 | | |
| Urethane | | Few cases | 132, 133 | | |
| Dinitrophenol | 1 1000 | Few cases | 129 | | |
| Probenecid | Benemid | Isolated cases | 115 | | |
| Phenylbutazone | Butazolidin | Isolated cases | 127 | | |
| n-methyl formamide | | Isolated cases | 134 | | |
| 6-mercaptopurine | | Few cases | 135 | | |
| Promazine | Sparine | · Isolated cases | 52 | | |
| Phenobarbital | 1 1111 | Isolated cases | 123 | | |
| Chlorambucil | Leukeran | Isolated cases | 128 | | |
| Diethylstilbestrol | | Isolated cases | 124 | | |
| Propylthiouracil | | Isolated cases | 114 | | |
| Quinacrine | Atabrine | Few cases | 125 | | |
| Metahexamide | | 1:200 | 141 | | |

cholestasis was not present, as with chlorpropamide, and electron microscopically no alteration of the microvilli was noted. Other cases seem to suggest that metahexamide jaundice belongs to the previous group.

The predominantly vascular involvement produced by urethane, ¹⁸², ¹⁸⁴ and the necrosis following the intake of drugs used in treating cancer or leukemia, ¹⁸⁴, ¹⁸⁵ should also be listed here.

5. Hepatic cancer: In recent years, primary hepatic cancer has attracted increasing interest, possibly as a reflection of increased incidence in the temperate zone. Industrial products and poisons such as pesticides have been accused of producing cancer in experimental animals.^{136, 137} Drugs have not been considered carcinogenic so far, with the exception of Thoro-

trast, given years ago for radiologic demonstration of liver and spleen. Since some of the drugs listed in the previous groups may produce post-necrotic cirrhosis, and since this is frequently associated with primary hepatic carcinoma, this question deserves further attention.

THE FUTURE

The future is bound to bring more rather than less of drug-induced hepatic injury. The crucial question for patient and physician is the risk involved. The answer entails the evaluation of the hepatotoxicity of a drug and the avoiding or minimizing of an injury with a known hepatotoxic agent. The evaluation of the toxicity will be facilitated by (1) careful collection of the clinical observations, (2) clarification of the nature of the injury, best done by liver biopsy, (3) improvement in communication as to the type of injury by standardization of the description and nomenclature of

Table 4

Incidence, Mortality, Dose Relation, Animal Experiments and Value of Hepatic Tests in Various Groups of Drug-Induced Hepatic Injuries

| | Metabolic Poisons | Cholestatic Drugs | Drugs Producing Hepatitis Picture | Unclassified Drugs | Carcino- genic Agents |
|-----------------------------------|----------------------|----------------------|---|-----------------------|-----------------------------|
| Incidence in persons exposed | High | Low | Very low | Very low | ? |
| Mortality | Dose dependent | Very low | High | Variable | ? |
| Dose relation | + | Not clear | Not clear | ? | ? |
| Reproduced in animals | + | 0 | ? | 0 | + |
| Tests indicate imminent danger | + | Suggestive | Not established | Not established | 3 |

hepatic lesions, and (4) thorough animal experimentation in several species, including dogs. The problem of hypersensitivity requires clarification—for instance, the reduced tolerance in some persons may be explained by genetic variations in enzymatic activity. Moreover, the therapeutic value of desensitization by administration of smaller doses remains to be established.

From the available information, the potential risks can be predicted with greater certainty in the first three groups than in the unclassified lesions and the potentially carcinogenic group (table 4). The metabolic lesion characterized by fatty metamorphosis and centrolobular necrosis presents a simple problem because of its regular occurrence and obvious dose relationship. The major problems are the two other groups, in which the dose relation is doubtful but the incidence is low and the hepatotoxic effect is therefore recognized only if many patients have been treated. The incidence, in general, seems to be higher with the group of cholestatic drugs. However, mortality or permanent injury is rare. In contrast, in the group with the virus hepatitis-like picture, the incidence is very low but, if hepatic

injury develops, it is very dangerous. Probably less hesitancy is indicated in prescribing the cholestatic drugs than those of the hepatitic group. The latter should be used because of their inherent therapeutic value only after full consideration of the potential danger. Their continued need might stimulate the development of derivatives with fewer hepatotoxic side effects. The use of a potentially dangerous drug is obviously discouraged if an equally effective, nontoxic alternative is available.

Avoidance of the injury or its spread depends upon the establishment of laboratory criteria for imminent danger. This is apparently simple with the metabolic or poisonous group. It is still too early to establish laboratory danger signals for the other drugs. It seems justified to suggest periodic (possibly weekly) determination of the serum activity of alkaline phosphatase and transaminase, together with bilirubin in the blood and urine, and discontinuation of the therapy when abnormal results occur. Such a program requires extensive laboratory services, which will be all the more justified the greater the known risk of prescribing a drug.

SUMMARIO IN INTERLINGUA

Injuria hepatic inducite per drogas es un phenomeno que subleva multe problemas. Un de istos es le establimento de un relation causal inter le morbo hepatic e le administration de drogas. Le sequente difficultates occurre in le establimento del etiologia de injuria hepatic causate per drogas: (a) Le hepate participa in multe reactiones systemic de maniera que alterationes laboratorial e histologic es possibilemente non le effecto del droga sed plus tosto del subjacente morbo pro le qual le therapia esseva instituite; (b) hepatitis e ictero pote resultar ab un seral hepatitis incidental; (c) le morbo hepatic es possibilemente independente del pharmacotherapia; (d) historias del administration de drogas es frequentemente pauco digne de confidentia; (e) le restringite lista del typos de reactiones del hepate in le presentia de agentes injuriose rende difficile establir le effecto de un droga specific; e (f) le criterios del alterationes morphologic in morbo hepatic non es standardisate. Plure strategias pote esser usate in establir le etiologia de injurias hepatic causate per pharmacos: (a) Le incidentia relative de injurias hepatic es importante, sed in le caso de multe drogas illo pote esser basse; (b) il occurre que tests hepatic deveni anormal post le administration de doses experimental; (c) le re-administration de un droga suspecte reproduce possibilemente le lesion o al minus certe manifestationes de injuria hepatic; (d) le tableau histologic es possibilemente de assistentia in identificar le lesion, sed frequentemente illo non es characteristic; e (e) le reproduction del lesion in animales es un forte prova secundari.

Iste modos de strategia ha permittite compilar un lista de entitates pathologic le qual es hic presentable con attention special prestate a ille entitates que esseva incontrate recentemente:

1. Zonal alterationes hepatocellular sin reaction inflammatori—con intoxication per tetrachloruro de carbon como exemplo typic—es producite peincipalmente per drogas que on deberea considerar como venenos que produce alterationes metabolic, Altere organos, particularmente le ren, es frequentemente afficite. Le incidentia es alte, e le magnitude del injuria depende del dosage. Le alterationes morphologic e functional es facile a reproducer in animales.

2. Cholestasis intrahepatic es producite per un gruppo de drogas sin characteristicas chimico-structural commun. Isto vale pro un basse numero de patientes

exponite a tal drogas. Chlorpromazina es un bon exemplo. Le functiones e le structura del cellulas hepatic non es injuriate a grados significative. In le majoritate del casos, un transiente inflammation portal es notate. Le mortalitate es basse. Le relation con le dosage es vage. Le lesion non pote esser reproducite in animales experimental. Illo representa probabilemente un defecto specific in le canaliculos biliari del hepate.

3. Necrose hepatic con reaction inflammatori le qual resimila hepatitis virusal ab le puncto de vista histologic es producite in rar patientes exponite a iproniazido, cinchophen, e altere drogas. Le mortalitate es alte, e massive necrose es producite. Experimentos animal remane ambigue. Le pathogenese non es cognoscite.

4. Un non-classificabile gruppo include un varietate de drogas con conspicue affectiones de organos altere que le hepate. Illos produce differente alterationes morphologic. Multes del existente reportos concerne casos individual. Experimentos con animales ha remanite sin valor.

5. Cancere hepatic debe probabilemente esser considerate, sed usque nunc solmente Thorotrast es implicate.

Pro evitar iste injurias on deberea haber criterios laboratorial del genere que es prestemente disponibile in le prime del supra-listate gruppos. Pro le altere drogas, determinationes del phosphatase alcalin e transaminase del sero es proponite insimul con mesurationes del bilirubina seral e urinari. Le therapia que es responsabile pro le resultatos anormal debe esser interrumpite.

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FAMILIAL RECURRING POLYSEROSITIS: A DISEASE ENTITY

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I. INTRODUCTION

FAMILIAL recurring polyserositis is a unique disease entity almost entirely limited to persons of Armenian, Syrian or Jewish ethnic origin. Janeway and Mosenthal in 1908 described a syndrome of recurrent abdominal pain in a Jewish school girl aged 16 years. All of her life she had suffered from recurring episodes of fever, leukocytosis and abdominal pain with abdominal rigidity and tenderness lasting one to two days and recurring at intervals of from one to four weeks. Siegal 2, 3 subsequently referred to this disease as "benign paroxysmal peritonitis," and Reimann,4 in his discussion of periodic diseases, included it as "periodic abdominalgia."

We believe that the previous concept of this disorder as a benign peritonitis should be broadened to include a polyserositis with recurring clinical manifestations involving an inflammation of the peritoneum, pleura, meninges or joints, within the hereditary pattern of this ethnic group. The term "familial recurring polyserositis" would more accurately characterize the nature of the disease, because the clinical and pathologic findings derive from involvement of multiple serous membranes.

The hereditary nature of the disease in Armenians and Jews has been reported by Siegal and Reimann.5 Recently Heller et al.6 have described it as a heredofamilial disease in persons of Mediterranean stock, and have contributed to the nomenclature of the disease the term "familial Mediterranean fever." Over 255 case reports can be accepted as valid examples of this disease. During the last decade the majority of such reports have appeared in the French medical literature under the title "La maladie périodique." 7-18

The disorder is an inborn error of metabolism, not sex-linked, transmitted by a dominant gene of incomplete penetrance. Victims have periodic episodes of severe abdominal, chest or joint pain, with fever, leukocytosis, and physical signs corresponding to the particular serosal membrane involved, i.e., peritoneum, pleura, or synovia of joints. We have studied 20 patients with this disorder, including 12 Armenians, seven Syrians and one Ashkenazi Jew. Fourteen patients were males and six-were females. The

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difficulty in establishing this new entity in the nosography of diseases has been the absence of laboratory criteria. It can be recognized as a clear-cut clinical entity, although the pathologic anatomy and the theories of pathogenesis are incompletely understood.

We shall summarize the clinical features of the disease before presenting the case reports of the patients we have studied. The presenting complaint is usually recurring paroxysms of severe abdominal pain. Fever is usually present, varying from 99° to over 104° F., and leukocytosis is a frequent finding. Episodes of pleuritic pain may occur in some patients, or the stethalgia may be associated with the abdominalgia. The patient may flex his thighs to relieve the abdominal pain, and may resist any movement of his body to avoid pain. Palpation of the abdomen elicits exquisite tenderness in a localized area or in diffuse areas. During episodes of pain, most patients refuse nourishment, and may vomit shortly after the attack has started. All patients recover completely from each episode of pain and are in normal health in the interval of weeks or months between attacks. The onset of the disease is often in infancy, but more frequently in the second or third decade of life. The disease is restricted virtually to the Armenian, Syrian and Jewish ethnic groups. Brick and Cajigas 22 have reported one case in an Italian male.

II. CASE REPORTS

Case 1. A Syrian male, now 34 years of age, began having episodes of abdominal pain at the age of 19. In the early years of his illness he had intermittent attacks of joint soreness in the knees, hips and elbows. He came to the United States at age 24 years and has been observed by us during the last nine years. When this patient was first seen we were not aware of the correct diagnosis. He was studied during many episodes of severe abdominal and chest pain. On several occasions the attacks were limited to the lower left chest, with suppression of breath sounds at the left lung base laterally.

After observation for two years an appendectomy was done. Several areas of the peritoneum were covered with small flecks of fibrin. The small intestine was studded with a fibrinopurulent exudate. Strands of fibrin stretched between the loops of bowel and over the diaphragmatic surfaces of liver and spleen. Culture of the peritoneal exudate was sterile. Microscopic examination of the appendix was normal except for a mildly edematous serosa with a thin infiltration of small round cells. The organs in the abdomen were entirely normal.

The appendectomy was done during an episode of severe abdominal pain when tenderness was localized in the lower right abdomen. The patient had a fever of 102° F., and the leukocyte count was 14,300, with 79% polymorphonuclears. Prior to the laparotomy we had examined the patient in several episodes of severe abdominal pain with generalized abdominal tenderness and rigidity atypical of appendicitis. In addition, during the previous year he had had an attack of left diaphragmatic pleurisy lasting three weeks, without severe abdominal pain. After the laparotomy the diagnosis of benign paroxysmal peritonitis was made. In subsequent recurring attacks the patient has been studied in an attempt to understand the pathogenesis of this disease.

The patient has remained in good health between the episodes of abdominal pain,

chest pain, or combined attacks. On three occasions a pleural exudate in the left costophrenic angle has disappeared promptly after the attack has subsided (figure 1). The interval between attacks has varied from three weeks to four months during the last nine years. The patient was treated with cortisone acetate in 1952. For a period of three months he was free from the recurring attacks. However, at the end of three months a recurring attack of abdominalgia was more extreme and persisted longer than had any previous episode. A similar experience followed the intramuscular use of adrenocorticotropic hormone. Para-aminobenzoic acid was used, with no apparent value.

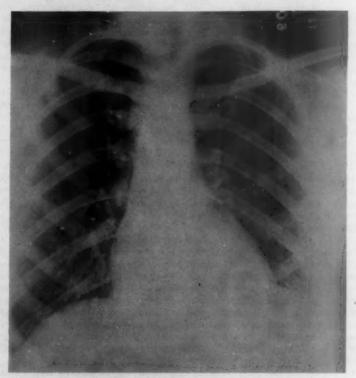


Fig. 1. Case 1. Pleural effusion in left costophrenic angle during an attack of chest pain.

In recent years the patient's recurring attacks have started with a prodromal period of from two to four hours. He is first conscious of a dull ache in the lower abdomen. As the attack progresses his pain spreads diffusely to other areas of the abdomen, and a pronounced rigidity of the abdominal musculature is present, along with an exquisite rebound tenderness. After from 12 to 14 hours the abdominal pain may become less intense while the patient breathes shallowly to splint the pleural pain at one or both sides of the diaphragm. On several occasions he has complained of pain referred to the shoulder tip. He has not had joint pains since coming to this country from Lebanon 10 years ago. The abdominal pain has been ameliorated by the slow intravenous injection of 400 mg. of tetraethylammonium chloride (TEAC). Because of the inconvenience of intravenous injection of TEAC, the patient was

instructed to inject subcutaneously 5 to 15 mg. of hexamethonium bromide. The latter therapy has lessened the abdominal pain for short periods of time, usually less than two hours in duration. On numerous occasions the stethalgia has been so severe that it required intercostal block anesthesia on one or both sides of the lower chest wall. Many of the episodes are accompanied by fever of from 99 to 104° F. However, his temperature has remained normal during a few periods of severe

abdominal or chest pain.

Extensive laboratory studies have been done during the last nine years. On one occasion the serum bilirubin was slightly elevated (to 1.3 mg.). In almost every attack of abdominal or chest pain the patient has a bilirubinuria, with a moderate to strongly positive Harrison spot test for bile. The leukocyte count is not always elevated during attacks. The sedimentation rate is usually high. Urinalyses have been normal except for one instance of gross and microscopic hematuria in 1950. Urea clearance and phenolsulfonphthalein excretion have been normal. Chromatography of the urine in the phenolic acid system has been normal between attacks, but has revealed a markedly diminished excretion of all elements during the attacks. An L.E. test was negative; an eosinophil count was 35 during an attack. Serum electrophoresis, bromsulfalein, cephalin-cholesterol and thymol flocculations were normal. Blood glucose, nonprotein nitrogen, serology, transduodenal biliary drainage, urinary porphobilinogen, serum amylase, electrocardiogram, electroencephalogram, blood and urine cultures, agglutinations for brucella and enteric pathogens have been normal. When the patient was first seen, Entamoeba histolytica and Giardia lamblia were identified in his warm stools. Repeated stool examinations have been normal since therapy for the amebiasis in 1950. The serum cholesterol was 160 mg., with 78% cholesterol esters. The intravenous hippuric acid liver function test was 0.2 gm. during an attack, and 1.2 gm. during a normal interval. Needle biopsy of the liver was done, with a normal report from the tissue study.

Spinal fluid protein has been elevated on three occasions, to 78, 64 and 66 mg., with a positive Pandy. During an attack with symptoms limited to the right chest, the spinal fluid protein was 53 mg., with a negative Pandy. Spinal fluid cell count,

sugar, chlorides and mastic have been normal.

Roentgen studies during attacks of abdominal pain have shown an abnormal pattern of motility through the small intestine, with delayed transit of barium and segmentation. Plain film of the abdomen during an attack has shown a marked distention of loops of small bowel with air. Intravenous pyelograms, cholecystograms and barium enema have been normal. The transit of barium through the small intestine has been normal in the interval between attacks. Chest x-rays were usually negative, but a transient pleural effusion in the left costophrenic angle has been found on three occasions.

The patient has one child 10 years old. However, an ensuing sterility has developed, with no change in libido or secondary sexual characteristics. The sperm count is low, with absence of sperm motility. A testicular biopsy showed absence of spermatogenesis. Studies of plasma steroids, 24-hour urinary 17-ketosteroids and 17-hydroxysteroids were normal. Although the testicular biopsy was done under a general anesthesia, the patient developed an attack of right chest pain after awakening from the anesthesia. There was no abdominal pain with this attack, although his urine was positive for bile by the Harrison spot test. The patient had previously demonstrated a similar precipitation of pain attacks after the needle biopsy of the liver and after three of his five spinal fluid aspirations.

The patient continues with recurring episodes of peritonitis and diaphragmatic pleurisy at grossly irregular intervals. His attacks seem to be more severe and prolonged in the late autumn and early winter seasons. At times the interval may assume some regularity, for a succession of three to five attacks every two weeks.

The longest period free from a major episode has been four months. However, minor abortive symptoms of abdominal pain without fever occurred several times in this relatively "free" period.

Comment on Case 1: This patient has a younger brother living in Lebanon who began having similar recurring episodes of joint and abdominal pains. The brother's attacks began at age 17, and continue at irregular intervals, although reported to be of less intensity than the disease in our patient. We have observed this patient in approximately 80 separate episodes of pain during the last nine years. He has evidence of peritoneal, pleural and meningeal irritation, as well as the history of prior joint pains and the familial incidence in his brother. These facts have led us to believe that the pathologic anatomy involves a polyserositis. Certainly a diagnosis limited to a benign peritonitis does not encompass the symptoms from other serosal involvement. His episodes have recurred irregularly, rather than with any fixed periodicity. The precipitation of attacks by needle biopsies of liver, testes and spinal fluid is an interesting phenomenon. Finally, the development of sterility in the patient may be related to this chronic recurring disease. To judge by prior reports in the French medical literature, 8, 10 sterility may prove to be a complication of familial recurring polyserositis. This patient is the first case of the disease reported with elevation of spinal fluid protein. He has had no clinical sign of meningeal irritation. The electroencephalogram and neurologic examination have been normal.

Case 2. This 46 year old Arab male was born in Syria and began having attacks of polyserositis at the age of 23 years. During the first four years his episodes were limited to monthly recurrences of diaphragmatic pleurisy. In later years the onset came as a dull pain in the epigastrium, progressing to a generalized tenderness in the lower abdomen. Fever is associated with the pain; vomiting has occurred on the second day when the attacks were severe. The patient has noted light colored stools and dark urine during several attacks. Prior to 1949 the differential diagnoses considered were pulmonary tuberculosis, pulmonary infarcts and chronic cholecystitis. In 1949 appendectomy and cholecystectomy were done. The appendix was normal, and the gall-bladder did not contain stones. There was an acute inflammatory exudate in the area of the gall-bladder, with fibrin and focal areas of leukocytes on the serosa.

The episodes of pleural and peritoneal pains continued after the operation. Four years later the patient became moderately icteric. A second surgical exploration was avoided when the diagnosis of polyserositis was made. In subsequent attacks there has been no clinical icterus, although the qualitative test of his urine for bilirubin has been positive. A small amount of pleural fluid has been present in the right costophrenic angle on two occasions. Needle biopsy of the liver was normal, although the procedure was followed by an exacerbation of the diaphragmatic pleurisy for one week. At the present time his episodes have continued for 23 years. The attacks may occur every three weeks with considerable regularity for long periods of time. The patient became a father two years ago and has no evidence of sterility. He has an abnormal pattern of small intestine motility during attacks, but has a normal roentgen examination of the intestine in the interval free from pain. His chest x-ray has a platelike atelectatic density above the right diaphragm. The urinary

function studies are normal except for suppression of phenolic acid excretions in the urinary chromatogram. The plasma fibrinogen has been elevated slightly (to 492 mg.), and the quantitative urinary urobilinogen was 1.63 units. Intravenous hippuric acid excretion was 0.64 gm. Bromsulfalein and liver flocculations were normal.

Comment on Case 2: This patient's brother, now 44 years of age, had entirely similar attacks of pleural and peritoneal pain for a period of eight years, starting at age 25. Heller et al.⁶ have doubted the occurrence of a complete remission in this disease. After interviewing our patient's brother, we believe he confirms the familial incidence of polyserositis, although he has not had a recurrence during the last 11 years. Case 2 represents an instance of considerable regularity of the presenting attacks, with episodes of both abdominalgia and stethalgia. Evidence of pleural and peritoneal exudation has been obtained.

Case 3. A 28 year old male of Armenian descent was first seen in our hospital at age six. He had had his first attacks of pain at two years of age. As a child, the onset was an upper abdominal pain, gradually increasing in intensity for 15 hours. He would draw his legs up on his belly and be afraid to move, and would request persons around him not to touch him. He refused all food or water on the first day of an attack. His appendix had been removed at age four years. During an attack at age six years, his leukocyte count was 34,800, with 82% neutrophils.

These episodes of abdominal pain, rarely combined with pleural pains, have continued at irregular intervals throughout the patient's lifetime. During the last four years he has been observed frequently during episodes of typical abdominalgia with rigidity of the abdominal musculature, rebound tenderness, dehydration, hypo-

peristalsis and oliguria.

Case 4. A female Armenian, age 29 years, sister of case 3, had the onset of severe abdominal pain before the age of two. Her appendix was removed at five years of age. She was first seen in our hospital two years later because of the recurring abdominal pains which had not been relieved by the appendectomy. Her attacks of abdominal pain were similar to her brother's, occurring with regularity every month. After menarche at age 14, the attacks of abdominal pain decreased in intensity but recurred several times each year. At age 20 she was seen because of dysmenorrhea and irregular menses of seven days' duration. Spherocytes and a prevailing microcytosis were seen in the blood smear. There was no sickling. A splenectomy was done for a diagnosis of congenital hemolytic anemia with repeated hemolytic episodes. A biopsy of the liver was normal. Extensive adhesions between the spleen and diaphragm were found.

Following the splenectomy the patient continued with intermittent episodes of abdominalgia, and was considered to be neurotic. During a period of medication with prednisone her attacks of pain were delayed for several weeks. At the present time the abdominal pain is less frequent and less severe than during her childhood. She has developed a deep keratitis of the left eye, uveitis and secondary glaucoma

of the right eye, etiology undetermined.

Comment on Cases 3 and 4: This Armenian brother and sister present a familial history of paroxysmal peritonitis beginning in their early childhood. Appendectomy at an early age did not prevent the recurring attacks of abdominal pain throughout their lifetimes. In retrospect, the splenectomy for congenital hemolytic icterus undoubtedly was not warranted by the

diagnostic criteria. The finding of a perisplenitis and adhesions to the diaphragm raises the question whether repeated episodes of diaphragmatic peritonitis leave such sequelae in the abdomen in this chronic disease.

Case 5. A 56 year old male, born in Russian Armenia, developed recurring attacks of chest and abdominal pain at age 24. He was first seen in our hospital at age 30, when he had a transitory pleurisy with effusion. Four years later his appendix was removed during one of his episodes of abdominal pain. A pleural effusion occurred during the postoperative convalescence. Abdominalgia and stethalgia have recurred at intervals of from two to six weeks during the last 20 years. In several hospitals of the area he had been considered to be a psychoneurotic of the hypochondriacal type, possibly a "segmental neuralgia." In spite of his atypical abdominal symptoms, he has been explored surgically in several hospitals. Cholecystectomy, liver biopsy and exploratory operations have not exposed any pathologic state in the abdomen.

Case 6. A 29 year old female born in Hungary of Jewish Ashkenazi ethnic subgroup, had the onset of abdominal pains at eight years of age, recurring at intervals of four weeks. The attacks ceased while she was interned in a concentration camp during World War II. The attacks returned at age 18 and have continued to this time, except during a pregnancy eight years ago. An appendectomy three years ago was followed by an exacerbation of severe abdominal pain lasting six weeks. The appendix was normal, but a small amount of fibrinous purulent exudate was found over the serosa of small bowel mesentery and the serosa of the

Case 7. Now 35 years old, this Armenian male has had attacks of abdominal pain beginning before he was two years old. Appendectomy was done at age two years. The episodes of pain have recurred about eight times a year, and last two to three days. During the attacks he is constipated and anorexic, and the pain is

aggravated by eating.

Case 8. The patient was a 36 year old male Arab, born in Jordan. At age 33 he had had the onset of severe abdominal pains simulating intestinal obstruction, lasting from one to seven days. The leukocyte count was 41,000, with 86% neutrophils. In one episode his serum bilirubin was elevated to 2.1 mg. The cholesterol was 168 mg., and the ester fraction was 85%. The test of urine for bile was positive, and diminished as the attacks subsided. Extensive laboratory and roentgen studies were normal, except for slow motility of barium through the small intestine and segmentation during attacks of abdominal pain.

Case 9. A 28 year old Syrian male had had the onset of recurring attacks of severe abdominal pain five years before. Two years later an appendectomy was followed by an exacerbation of the abdominal pain. The appendix was normal, but flecks of purulent material were found over the intestinal serosa. Culture of the pus was sterile. The patient's attacks have continued with increasing regularity every seven to 10 days, and last from 36 to 48 hours. During one attack the serum bili-

Case 10. A 40 year old male of Armenian descent had had attacks of pleural pains at 22 years of age. He was studied carefully in Army hospitals, and later by the Veterans Administration. Within two years he developed severe epigastric pains with chills. He secures relief by lying supine. Movement of his body in either direction causes aggravation of the pain and reference of pain to the shoulders. He had an abdominal laparotomy in a Veterans Hospital and no abnormalities were found. During the last 10 years his attacks have come regularly every two weeks, and last from one and one-half to two days.

Case 11. The patient was a 24 year old male born in Detroit of Syrian ancestry. His abdominal pains had recurred many times before his appendix was removed at age three years. Since the age of 11 years he has had pains in the lower chest which may be associated with the abdominal pain. He frequently vomits at the onset of an attack and then becomes constipated. During the last six years the attacks have recurred at intervals of from four to six weeks. This chronic recurring disease has been an economic handicap in his life. He married at age 20 and has two children.

Case 12. An Armenian male who is now 32 years of age had a severe abdominal pain at age 26. The initial attack lasted 36 hours. He had no further episodes for one year, then had two mild attacks. During the last three years the abdominal pain has recurred almost every month. The abdominalgia is diffuse, but may be especially severe in any quadrant of the abdomen. He passes flatus at the inception

of the attack and is constipated thereafter.

Case 13. This 54 year Armenian male had the onset of the disease at age 42 years. Following an appendectomy the attacks of upper abdominal pain continued to recur every two weeks, with chills and fever to 104° F., gradually subsiding, leaving the patient weakened for about two days, after which he would feel perfectly well. In 1951 his white blood cell count was 16,400 during an attack. There was elevation of the right leaf of the diaphragm, with a density thought to be due to atelectasis in the superimposed lung tissue. A chest x-ray a few days later showed the lung changes to have subsided. The omentum was found to be adherent to the edge of the liver. Over the dome of the liver were numerous thick adhesions to the diaphragm. The gall-bladder was normal. The patient continues to have regularly recurring episodes of abdominal pain every 10 to 14 days, lasting one to two days.

Case 14. A 31 year old Syrian has had regularly recurring abdominal pain every month since the age of 22. The abdominalgia is associated with fever, nausea and vomiting. The symptoms subside in two days. There is decreased gastrointestinal

motility during the hours of abdominal pain.

Case 15. A 34 year old female of Armenian descent had the onset of abdominal pains at 14 years, beginning three months before the menarche. She has continued to have five or six attacks each year, characterized by abdominal pain beginning in the lower abdomen and radiating to all areas. Her temperature has been elevated to 103° F. Attacks seemed to be less frequent and less severe after her first

pregnancy.

Case 16. A 16 year old Armenian schoolgirl began to have episodes of abdominal pain when she was one year old. She was first seen in our hospital at three years of age, when the attacks had become more frequent and recurred as regularly as every seven days. Her leukocyte count was 13,000, with 74% neutrophils during an attack. She had an appendectomy at age nine, without relief. Menses had started at 10 years and 10 months, and were regular. On one examination a few red cells and pus cells were found in the urine, but cultures and pyelograms were normal. patient walks with a limp during the episodes of abdominal pain, being unwilling to lie down.

Case 17. A 12 year old Syrian girl had onset of the disease at five years. Episodes of periodic abdominal pain occurred every two to three months and later became more frequent, occurring every two to three weeks and lasting from 12 to 24 hours. Free fluid in the peritoneum had been found during an otherwise normal laparotomy at seven years. Her father's brother has had similar recurring abdominal pains for many years. No evidence of the disease has been recognized in the patient's four older siblings. Her episodes of abdominal pain have occasionally been preceded by angioneurotic edema of the hands and feet,

Case 18. A 35 year old Armenian female had the onset of abdominal pains at age 18. These episodes have been increasing in intensity, recurring regularly every month but not in relation to the menstrual cycle. At 24 years of age she had pleurisy and recurrent chest pain, lasting two to three days in each attack. After six years of marriage, conception has not occurred and the patient is a sterility problem.

Case 19. This Armenian male, now 33 years old, had the onset of right posterior chest pains at 18 years of age. These episodes recurred several times while he served in the Army. His fever rose to 104° F., but the distress subsided in two to three days. He had two to four attacks of chest pain each year until he was 29 years old, when the pattern of pain shifted to his lower abdomen. Walking or standing increased the pain, bending forward relieved it. The interval between attacks has shortened in recent years. Diffuse abdominal pain and tenderness are now the prominent symptoms.

Case 20. A 30 year old male of Armenian-Greek-Ukrainian extraction was jaundiced three times between ages 12 and 14 years. At 21 years he developed epigastric pain lasting from three to six days and recurring every three to six months. The attacks have become more frequent in the last six years, with a cycle of recurrence every 14 days. The abdominal pain intensifies for several hours, and is most severe in the right upper quadrant and referred to the right shoulder. His breathing is shallow to avoid pain. There is minimal pleural thickening over both lower lung fields, with slight blunting of the right costophrenic angle.

III. COMMENT

1. Clinical Diagnosis. The patients with familial recurring polyserositis present a dramatic tableau of symptoms. Whether the patient is seen first in an attack of chest pain or in exquisite abdominal pain, the clinical picture is usually atypical of any diagnoses ordinarily considered. Fortunately, the abdominal crises are usually terminated within 48 hours, and the majority of patients have learned to refuse unnecessary abdominal operations. The disease is a chronic one, and the history of recurring attacks over periods of as long as 32 years (case 5) encourages a long period of observation before surgical exploration of the abdomen is recommended.

Table 1 summarizes the clinical features of the patients we have studied. A history of familial incidence was recorded in five of the 20 patients. Because of wars and persecutions, many of the Armenian patients knew nothing about their family history. The age of onset was before the third decade of life in the majority of patients. Sturtz and Burke ¹⁰ reported the first cases in American pediatric literature. Their two patients, an Armenian and a Syrian, had the onset of the disease at three years of age. The Armenian male who described his first attack at age 42 (case 13) has had entirely typical episodes of this disease during the last 12 years.

Severe abdominal pain has been the most common form of the attacks. Every patient has had a changing pattern of abdominal pain. The pain has often been prominent in one area of the abdomen, frequently the epigastrium or right upper quadrant. Usually the pain spreads diffusely over the entire abdomen, with involuntary rigidity of the abdominal wall. There may be

an initial feeling of fullness in the abdomen. Many patients vomit; others become constipated throughout the course of the attack. In most cases, rebound tenderness gives rise to alarm if the diagnosis is not understood by the physician.

Although all of our patients had abdominal crises, it is to be emphased that 12 of the 20 patients also had attacks of chest pain. Often the point of origin of the abdominal pain was in the lower thorax, spreading downward over the entire abdomen. Cases 1 and 2 were observed in many episodes of diaphragmatic and pleural pain with no associated spasm of abdominal muscles. In these two patients the diaphragmatic pleurisy seemed to persist longer than the episodes of abdominal pain. Often the pain radiates to both shoulders. Just as the patient avoids body movements during the abdominal attacks, he tries to splint his breathing when he has chest pain. Respiratory excursions are shallow and rapid. The chest pain may shift

TABLE 1

| | Case No. | Sex | Pres- ent Age | Age at Onset | Ethnic Group | Familial History | Ab- dominal | Chest Pain | Joint Pain | Interval Between Attacks | Duration of Attacks | Regular ity of Attacks |
|-------|-------------|-----|---------------------|--------------------|-----------------|---------------------|----------------|---------------|---------------|--------------------------------|---------------------------|------------------------------|
| I. S. | 1 | M | 34 | 19 | S | . + | + | + | (+) | 1-4 months | 4-6 days | 0 |
| A. S. | 2 | M | 46 | 23 | S | + | + | + | 0 | 2-3 weeks | 4 days | + |
| A. F. | 3 | M | 28 | Under 2 | A | + | + | (+) | 0 | 1 month | 2 days | + |
| A. R. | 4 | F | 29 | Under 2 | A | + | + | 0 | + | 2-8 weeks | 1 day | 0 |
| H. M. | 5 | M | 56 | 24 | A | 0 | + | + | 0 | 2 weeks | 4 days | +- |
| M. F. | 6 | F | 30 | 8 | J | 0 | + | Rare | 0 | 1 month | 2 days | (+) |
| H. B. | 7 | M | 35 | Under 2 | A | 0 | + | Rare | 0 | 1 month | 2 days | 0 |
| Y. S. | 8 | M | 36 | 33 | S | 0 | + | Rare | 0 | 4-6 months | 1-7 days | 0 |
| W. S. | 9 | M | 28 | 23 | S | 0 | + | 0 | + | 2 weeks | 2 days | + |
| L. D. | 10 | M | 40 | 22 | A | 0 | + | (+) | 0 | 2 weeks | 1 days | + |
| R. B. | 11 | M | 24 | Under 2 | S | 0 | + | + | 0 | 2-3 months | 2 days | 0 |
| K. K. | 12 | M | 32 | 26 | A | 0 | + | 0 | 0 | 1-2 months | 1 days | (+) |
| E. K. | 13 | M | 54 | 42 | A | 0 | + | 0 | 0 | 2 weeks | 2 days | + |
| G. K. | 14 | M | 31 | 22 | S | 0 | + | 0 | 0 | 1 month | 2 days | 0 |
| L. D. | 15 | F | 34 | 14 | A | 0 | + | 0 | 0 | 2 months | 2 days | 0 |
| S. D. | 16 | F | 16 | Under 1 | A | 0 | + | 0 | 0 | 1-3 weeks | 2 days | 0 |
| D. E. | 17 | F | 12 | 5 | S | + | + | 0 | 0 | 2-3 months | 1 day | 0 |
| E. M. | 18 | F | 35 | 18 | A | 0 | + | . + | 0 | 1 month | 2 days | 0 . |
| W. K. | 19 | M | 33 | 18 21 | A | 0 | + | + | 0 | 2-4 months | 2 days | 0 |
| M. A. | 20 | M | 30 | 21 | A | 0 | + - | Rare | + | 2 weeks | 2 days | + |

S-Syrian A-Armenian J-Jew ()-formerly

downward after several hours, or combined abdominal and chest pain may occur.

A suppression of breath sounds at the lung bases usually accompanies the episodes of chest pain. The finding of platelike atelectasis in the lung base of three patients is due to the splinting of the diaphragm in repeated episodes of the chronic disease. Eight of the patients had splenomegaly, diagnosed by palpation, percussion or roentgen examination. Hepatomegaly was found in three patients. It is suspected that a careful technic of percussion during the attacks would yield a higher incidence of liver and spleen enlargement.²⁰

Attacks of joint pains have been described in the foreign medical literature as a prominent manifestation of the disease.^{6, 9, 11, 18, 15, 16, 17, 21} Only four of our patients described episodes of arthralgia. In each patient this

occurred in the early course of the disease, and arthralgia was superseded by abdominal or chest attacks. Our patients did not exhibit any skin manifestations. Heller et al.⁶ described an "erysipelas-like erythema" on the lower extremities. Case 17 may have had an angioneurotic edema of hands and feet preceding an occasional episode of abdominal pain. Mamou ¹⁷ described giant urticaria as a premonitory sign.

2. Roentgen Findings. The importance of diagnostic roentgen studies during the acute phase of this disease has not been adequately explored.

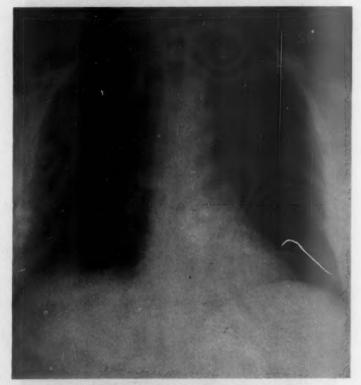


Fig. 2. Case 5. Linear atelectasis in lung bases. The patient had a 32-year history of recurring attacks.

Siegal ⁸ reported one case with fluid at the right costophrenic angle. Distended loops of small bowel have been observed in the plain film during abdominal crises. ^{6, 22} Reimann ⁴ and Bickel and Lasserre ²⁸ reported motor abnormalities of small intestine transit.

We have found in two patients (figure 1) a transient pleural effusion at the costophrenic angle during episodes of chest pain. The physical signs disappear within a few days. Progress x-rays have been normal in the interval between attacks. In three other patients a linear atelectasis at the lung base was seen in the chest films. The patient in figure 2 has had recurring attacks of diaphragmatic pleurisy for 32 years. Splinting of his diaphragmatic excursion has been responsible for this type of atelectasis.

Nine patients x-rayed during abdominal crises have had air distended loops of intestine. In several instances the appearance simulated small bowel obstruction. In spite of severe abdominalgia, 13 patients have had



Fig. 3. Case 1. Delay in transit of barium through the jejunum during an episode of abdominal pain. Roentgen film taken at two and one-half hours.

barium studies of small intestinal motility during attacks of abdominal pain. These studies demonstrated a nonspecific disorder of motor function. Transit time was delayed (figure 3), and barium frequently did not pass through the proximal jejunum in less than three and one-half hours. Segmentation (figure 4) occurred atypically, with connecting strands of barium between the segments. There were abnormal variations in the caliber of the small intestine, and loops with frank segmentation in some areas. In place of

the normal serpentine loops, the small intestine became angulated in bizarre directions. Eight of these patients studied during pain-free intervals had reverted to a normal pattern of small intestine motility. Although these roentgen findings are nonspecific, they add to the few diagnostic studies as yet available to aid in the diagnosis of this disease.

Heller et al.6 reported one case of extensive bone and joint involvement, with roentgen evidence of destruction of the knee and changes in the x-ray



Fig. 4. Case 5. Abnormal motor pattern of small intestine at nine hours, with discontinuous barium column, some flocculation, wide ileal loops and delayed transit.

appearance of the humerus. Mamou ¹⁷ reported from Siguier a case of osseous rarefaction in the phalanges of the hand. No patient in our series suffered from chronic arthritis. We have not made an intensive search for joint lesions by roentgen study.

3. Laboratory. A precise diagnosis of this disorder has been difficult because of the absence of laboratory criteria. In most of the reported cases a plethora of normal laboratory examinations has been recorded. Many of

the abnormal laboratory tests are entirely nonspecific, such as an increase in the erythrocyte sedimentation rate, a fall in the eosinophil count during the attack of pain, and a leukocytosis frequently present during the febrile phase. In his monograph, Mamou ¹⁷ reported slightly abnormal findings in serum electrophoresis. We have not confirmed this in the electrophoresis of the sera of eight patients. Benhamou's triad ¹¹ included increased serum fibrinogen, elevated titer of antistreptolysin O, and haptoglobulinemia. In four patients we have found the plasma fibrinogen to be elevated during an attack and normal at other times. However, Foster and Whipple ³⁶ in 1922 showed that fibrinogen elevations occur in acute inflammatory conditions. It would appear that this is another nonspecific phenomenon.

Six of our patients have had an increase in the serum bilirubin during attacks. Three of them were recognized clinically as icteric. Seventeen patients tested in this series had positive bilirubinuria by the Harrison spot test during abdominal or pleural crises. Urinary porphobilinogen was negative in 10 patients. Liver flocculation tests in 13 patients and the bromsulfalein test in seven patients were normal. However, the intravenous hippuric acid test was low in six patients studied during attacks, and the quantitative urinary urobilinogen was increased in three patients. Three patients had cholesterol esters of over 78% at the inception of an attack, with a normal total serum cholesterol.

One patient of 10 studied had spinal fluid protein increased to as high as 78 mg. Pandy test was positive in this and in one other patient. Electroencephalograms were interpreted as normal in nine patients studied during recurrences of pain.

Foreign authors have included renal complications as sequelae of the disease. Cattan and Mamou ⁷ have considered albuminuria to indicate a poor prognosis. None of our patients has had albuminuria or azotemia. We have found renal function to be normal. Of particular interest to us has been the change in the chromatography of the urine during attacks. The chromatogram is reduced in all elements during attacks of pain. ²⁴ This phenomenon may be related to abnormal renal physiology, but the markedly decreased metahydroxyhippuric acid leads to the conjecture that it may be related to hepatic function.

4. Pathology. The pathologic anatomy of this disease is incompletely understood. Most of the information available has come from abdominal operations, usually performed before a precise diagnosis has been established. From these reports of abdominal operations it is apparent that the visceral and parietal peritoneum is involved in an acute inflammatory process during the attacks. Pleural exudates indicate that the pleura is similarly involved, and the increased spinal fluid protein in our first case may indicate that meningeal surfaces are affected. Mamou and Maret ²⁵ included the pericardium, and stated that the meninges were the only serosal surface not yet reported as being involved.



Fig. 5. Case 2. Pericholecystitis. Focal collections of neutrophilic leukocytes on perimuscular layer of gall-bladder. (× 105.)

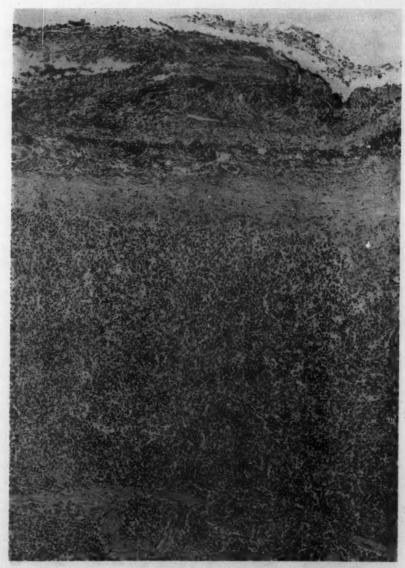


Fig. 6. Case 4. Fibrous perisplenitis. Capsule of the spleen is thickened and shows some nodular hyalinization. (×105.)

Advanced renal pathologic changes have been reported by several authors. 6,7,16,17,28,26 Siguier 18 commented that renal complications were "curiously absent in foreign publications." Mamou 16 reported the first case of amyloidosis as a cause of death in this disease, and stated that the liver, spleen, thyroid and kidneys were involved. Tuqan 27 recently described amyloidosis as the cause of the "nephropathy" in two necropsied cases. Mamou 17,25 has reported an endarteritis producing parenchymal renal infarcts. A review of pathologic material from our patients is in progress.

Fourteen of our patients have had 18 abdominal operations. These operations have included appendectomies, two wedge biopsies of the liver, one cholecystectomy, one gall-bladder biopsy and one splenectomy. From the reports available at our hospital and other institutions, no gross pathologic changes were found except sterile peritonitis, periappendicitis, perisplenitis, perihepatitis and pericholecystitis. Seven patients had a sterile culture of the peritoneal exudate. Needle biopsy of the liver has been done in three patients, with normal liver tissue reported. Figure 5 shows a section of the gall-bladder wall in case 2. The perimuscular layer of the gall-bladder had focal collections of neutrophilic leukocytes, without any apparent acute inflammation or necrosis of the muscle layers. The perimuscular layer of the gall-bladder had some increased fibrosis, lymphocytes and plasma cells. There were no gall-stones.

Reimann ⁶ has mentioned "how little cicatrization or thickening remains as residues of hundreds of insults during episodes over many years." The fibrous perisplenitis (figure 6) found in case 4 was nonspecific, but may have resulted as a sequela of recurring left diaphragmatic peritonitis. Abdominal laparotomy in case 13 demonstrated thick adhesions over the dome

of the liver and to the diaphragm.

IV. NOMENCLATURE

In Lebanon this disease is called "Armenian disease." 5, 28 Janeway and Mosenthal called it a paroxysmal syndrome. Siegal suggested that "benign paroxysmal peritonitis" called attention to its distinctive clinical features "until such time as classification becomes possible on a sound etiologic or pathologic basis." The first criterion has not yet been established, but the disease is known to be neither entirely benign nor limited to the peritoneum. Reimann included cases of this disease in a discussion of periodic diseases, and later 4, 80 he termed it "periodic abdominalgia." Siegal objected to this term, signifying recurring abdominal pain, as not adequately characterizing the clinical picture of the paroxysms of the disease. Reimann later added "periodic peritonitis" to the nomenclature.

French authors have objected to the connotation of "periodic." They have suggested that the paroxysms recur at grossly irregular intervals, varying from a few days to many months. For this reason Siguier used the title "La Maladie dite Périodique" (so-called periodic disease). 10, 13

Mamou ^{17, 25} suggested the name "Épanalepsie Méditerranéene," which means repeated Mediterranean attacks without definite rhythm. Bickel et al. ²⁸ reverted to the eponym of "the disease of Siegal-Cattan-Mamou." The most recent addition to the nomenclature has been "familial Mediterranean fever." Heller et al. 6 have based their sine qua non for diagnosis on the attacks of fever. We have observed patients with no fever during episodes of severe pain associated with the serositis. We also object to the implication of a geographic predilection. The familial predilection is to certain ethnic groups, rather than to a geographic locale.

Table 2 summarizes the historical deviations of the nomenclature of this disease. We propose to establish "familial recurring polyserositis" in the nosology of diseases for the following reasons: first, it has been established

TABLE 2

Nomenclature of the Disease

Paroxysmal Syndrome (Janeway and Mosenthal) 1908

Benign Paroxysmal Peritonitis (Siegal) 1945

Periodic Abdominalgia 1949 Periodic Peritonitis 1954 (Reimann)

La Maladie Périodique

La Maladie dite Périodique (Siguier) 1953

Épanalepsie Méditerranéene (Mamou) 1954 France

Familial Mediterranean Fever (Heller) 1955 Israel

Disease of Siegal-Cattan-Mamou (Bickel) 1957 Switzerland

"Armenian Disease" Syria

Familial Recurring Polyserositis 1959

as a familial disease; second, the attacks recur at irregular intervals, rather than periodically with a definite rhythm; third, on the basis of present knowledge, polyserositis most accurately characterizes the clinical nature of the disease. Attacks of serositis have been responsible for pain from the peritoneum, pleura and synovia of joints. Evidence has been presented that the meninges and pericardium may become involved. The term "familial recurring polyserositis" does not imply an etiologic diagnosis, as yet unwarranted. As Mamou ¹⁷ has stated, the disease is an autonomous clinical entity and not a syndrome.

V. DISCUSSION

Janeway and Mosenthal in 1908 presented their case study as an unsolved diagnostic problem. From the standpoint of pathogenesis, the

disease remains unsolved. Cooke 82 studied Janeway's patient 24 years later and considered milk allergy as an etiologic factor. Siegal 2, 3 felt that the evidence was strongly suggestive of allergy but not conclusive. Reimann 5, 30 suggested that a vasomotor or neurovascular disturbance might account for the signs of periodic disease. He described a slight cellular invasion of the myenteric plexus. Tuqan 27 in a clinicopathologic study of two necropsied cases questioned whether periodic disease is one of the collagen diseases. He compared the immuno-allergic features of collagen diseases to the distribution of amyloid in his case studies. Mamou 16 pointed out that all reports agree that the disease is not bacterial or parasitic in origin. Mamou suggested either a hyperallergic state of the patient, or an autosensitization of the patient, with antibodies formed against tissue modifications produced by a stress agent. Bickel and Lasserre 23 reported the inconstant finding of iso-agglutinins contrary to earlier reports. The most recent and convincing work on the pathogenesis of this disease has been the report of auto-immune antibodies by de Vries et al.33 This study described abnormal red cell membranes found in electron microscopy. In addition, patients with periodic disease had an agglutinin of the warm antibody type, not a hemolysin. The hypothesis proposed for the basic pathogenetic mechanism of the disease was an auto-immune mechanism developing on the basis of a constitutional abnormality, which manifests itself in defective structure of the red blood cells. No relation between the auto-immune mechanism and the clinical manifestations of serositis has been established.

An interesting phenomenon we have observed has been the apparent cause-effect relationship of needle trauma of serosal surfaces and the precipitation of attacks. Needle biopsy of the liver through the right seventh intercostal space seemed to initiate episodes of stethalgia and abdominalgia in two patients. The first patient reported in our series had an attack of diaphragmatic pleurisy immediately following needle biopsy of the testes under a general anesthesia. There was no abdominal pain or rigidity in this particular episode of chest pain; however, the test for urinary bilirubin was positive! Three patients in our series suffered prolonged attacks after abdominal operations. An interesting speculation is the relationship of such trauma to the development of attacks.

Of similar interest is the possible effect of pregnancy in ameliorating the intensity and frequency of attacks. Two patients in our series were improved during pregnancy. The remissions during pregnancy have been cited by several authors. 3, 4, 5, 6, 8, 23 The possibility of permanent remission of the disease has not been determined. The brother of case 2 seems to have had a sustained recovery for 11 years. Siegal 3 mentions that the father of one of his patients did not have attacks after the age of 61 years. Another of his patients, aged 63, had only mild episodes after the age of 58. It would seem that an accurate prognosis of the natural history of the disease will require further knowledge of its primary etiology.

There have been no successful therapeutic measures to prevent episodic recurrences. The evaluation of any drug must be prolonged to the point where simple coincidence or temporary spontaneous remission will not lead to unwarranted optimism. One of our patients seemed for several months to have been "cured" by cortisone. However, the exacerbation after the remission was more severe. We have given para-aminobenzoic acid to four patients without influencing the course of the attacks.34 We have found antibiotics, chlorpromazine, chloroquine, antihistaminics, prochlorperazine and quinacrine to be ineffective. As these patients return time and again in their agony of pain, the simple amelioration of their symptoms becomes a vexing problem. None of our patients has become overtly addicted to narcotics. It is surprising that many of them have not. If the attack of pain is limited to abdominalgia, we have found that tetraethylammonium chloride (400 mg.), slowly administered intravenously, may relax the involuntary rigidity of the abdominal muscles. However, a deep aching pain of only moderate intensity usually persists in the lower abdomen. Israel et al. 85 used this drug to obtain relief of chest pain in a variety of conditions, but we have found it to be ineffective if diaphragmatic pleurisy accompanies the lower abdominal pain. Tetraethylammonium chloride reversibly blocks both divisions of the autonomic nervous system. Because intravenous administration is necessary, its use by the patient is impractical. We have taught several patients to inject subcutaneously another ganglionic blocking agent, hexamethonium bromide, but its use in doses of 5 to 15 mg. is not effective if the attack of pain is severe. Pentolinium tartrate (Ansolysen) might be considered for oral use. However, we have not tried this drug because of the intestinal hypomotility often associated with this disease. We fear the effects of hypotension if the absorption of pentolinium was delayed and then released too rapidly. Undoubtedly a clearer understanding of its pathogenesis is imperative if a rational therapeusis is to be applied to this disease.

VI. SUMMARY

The clinical and diagnostic criteria of familial recurring polyserositis have been presented. It is likely to be another disease added to the list of inborn errors of metabolism. Its etiology and pathogenesis are incompletely understood, although its hereditary nature has been established in certain ethnic groups. Patients with this disease face serious economic and sociologic problems because of the seemingly interminable recurrences. The recognition of this entity must be made more widespread, and it is hoped that the grim prospect of its chronic recurrence will be lightened by further research.

SUMMARIO IN INTERLINGUA

Recurrente polyserositis familial es un clinicamente distincte disordine hereditari que occurre in armenios, arabes, e judeos. Le etiologia e le pathogenese de iste morbo non es cognoscite, sed on pote supponer que il se tracta de novo de un innate error metabolic.

In le vaste majoritate del patientes le morbo ha su declaration ante le tertie decennio del vita. Le proportion inter le sexos monstra un preponderantia mascule de approximativemente 2:1. Le morbo es characterisate per repetite episodios de acute serositis de duration restringite, afficiente abdomine, thorace, e articulationes (in descendente ordine de frequentia). Dolores e febre es symptomas cardinal, sed il occurre que le febre es minimal o absente.

Attaccos abdominal, que es le characteristica essential del morbo, presenta un tableau de peritonitis local o diffuse, accompaniate de varie grados de hypomotilitate intestinal e in casos extreme de ileus complete. Hepatosplenomegalia minimal es presente, usualmente determinabile solo post meticulose percussion del margine superior de sono mat pro le organos in question.

In coincidentia temporal con le acute episodios abdominal o post illos o, plus rarmente, como evento isolate, il pote haber pleuritis acute, usualmente con minor effusion pleural. Monoarthritis o polyarthritis acute ha essite describite como un aspecto integral del morbo, sed in nostre experientia affectiones del articulationes ha remanite limitate a un basse incidentia de arthralgias. In rar casos, altere membranas serose—per exemplo pericardiales e meningees—pote participar in le spectro inflammatori del morbo.

Usque nunc, nulle test diagnostic ha essite trovate. In nostre patientes, bilirubinuria—indicate per un positive test de Harrison—esseva trovate uniformemente durante le attaccos acute. Etiam leve grados de bilirubinemia esseva incontrate frequentemente. Leucocytosis de varie grados de severitate, con neutrophilia, es un observation constante. Un disturbate comportamento motori del intestino tenue esseva demonstrate roentgenographicamente durante le attaccos abdominal.

Le morbo se distingue per inpredicibile remissiones. Le prognose es generalmente bon, sed il ha reportos de un non ancora determinate incidentia de terminationes mortal con morbo amyloide del renes.

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FURTHER OBSERVATIONS ON THE MECHANISM OF ULCER PAIN * † ‡

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DIRECT chemical irritation by hydrochloric acid and disordered motor activity of the stomach and duodenum have been implicated in the causation of ulcer pain. The presence or absence of vascular engorgement of the mucosa in the region of the ulcer has also been related to ulcer pain. Many investigators have tended to support one or the other points of view without implicating other factors. Although the concept of direct chemical irritation has been the more commonly accepted one among gastroenterologists, physiologists have maintained that the mechanism for pain arising from any of the hollow viscera is some disorder of motor function.

To shed light on this problem, observations have been made during the last eight years on more than 500 patients concerning the mechanism of ulcer distress. The observations have included study of the effect of intragastric administration of 200 ml, of 0.1 N hydrochloric acid on the occurrence of ulcer pain in patients with active gastric or duodenal ulcer, the effect of vagotomy and autonomic-acting drugs on ulcer pain, the determination of the basal gastric secretory rate in patients with active and inactive peptic ulcer, and the study of the motor activity of the stomach and duodenum by intraluminal pressure recording, fluoroscopy, and simultaneous fluorocinematography. The purpose of the present report is to examine critically the theories concerning the mechanism of ulcer pain and their experimental support.

EARLIER OBSERVATIONS

The experimental observations of the past can be divided into two groups: those which relate ulcer pain to direct chemical irritation by hydro-

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chloric acid, and those which implicate abnormal gastrointestinal motility. Although Prout ¹ identified hydrochloric acid in the secretion of the stomach in 1824, the mechanism of its formation, ² as well as its role in the production of ulcer pain, remains controversial. In 1908 Bonninger ³ reported that instillation of hydrochloric acid reproduced the distress of peptic ulcer, and suggested this as a diagnostic technic for ulcers of the stomach. Hardt ⁴ repeated these experiments but could not relate ulcer pain directly to gastric acidity. Palmer ^{5, 6, 7, 8} reported that ulcer pain followed instillation of acid in a high proportion (approximately 90%) of patients with active gastric and duodenal ulcer who had experienced pain within the preceding 24 hours. If pain did not follow instillation of the first aliquot of acid, a second or third aliquot was added at 30-minute intervals. Palmer concluded that ulcer pain was the result of direct chemical irritation from hydrochloric acid.

Hardy 9 found that ulcer pain developed in many patients with active ulcers following the "acid test." However, he found that instillation of acid was not specific for ulcer pain, and that distress might occur following the acid test in patients with other diseases. Similar studies were carried out by Kinsella 10, 11 and by Bonney and Pickering. 12, 13 The latter investigators concluded that ulcer pain was not dependent upon gastric or duodenal tone or motility, but was a direct result of chemical irritation with hydrochloric acid. Titrimetric studies were also reported by Christensen 14 and Woodward and Shapiro. 15 During some of these studies, balloon kymograph tracings or intraluminal pressure measurements were used to study motor activity. 16 Motility has also been studied by adding barium sulfate to the hydrochloric acid and observing the motility by roentgen technics. 9-18

Faber ¹⁷ noted that ulcer symptoms were more likely to occur with juxtapyloric ulcers, and Hurst ¹⁸ suggested increased tension as the cause of ulcer distress. Carlson ¹⁹ and Christensen, ¹⁴ using gastrographic technics, related ulcer pain to the contractions of the stomach. On the other hand, Ortmayer, ¹⁶ using similar technics, failed to obtain evidence that gastric contractions were the common factor in ulcer pain.

Reynolds and McClure ²⁰ reported abnormal motor patterns on roentgen study in patients with ulcer distress. Wilson ²¹ attributed ulcer pain to contractions of the duodenal cap. Kinsella ^{10, 11} related pain to the presence of an inflammatory reaction with a rise in tissue tension, and concluded that ulcer pain was the result of squeezing on the inflamed sensitive tissues. Ryle ²² attributed ulcer pain to a general increase in gastric tone.

Dragstedt and Palmer ²⁸ noted that rubbing the serosa over an ulcer in a patient who was explored surgically under local anesthesia produced typical ulcer pain. Compression of the ulcer or traction on the duodenum also resulted in pain, which was accompanied by a deep circular contraction ring just distal to the ulcer, and was succeeded by similar spasms resulting in severe, cramplike pain.

The experimental studies in animals by Quigley and associates 24, 25, 26,

^{27, 28} indicate that the pyloric sphincter and adjacent regions behave as a unit. The sphincter is normally either relaxed or rhythmically contracting at a rate of five to seven contractions per minute. Coördinated activity of the antral "pump" results in evacuation of the stomach. Quigley suggested that " in the patient with an ulcer, gastric acid must act indirectly and produce pain by inducing abnormal motility in the region of the ulcer." ²⁸

Interest in the problem of ulcer pain was stimulated by the reintroduction of vagotomy in 1943 by Dragstedt ²⁹ for the treatment of duodenal ulcer. The most striking effect of vagotomy in a patient with chronic peptic ulcer was immediate relief of pain. ^{30, 31} Ruffin and White ³¹ reported that the most constant physiologic effect of vagotomy was an alteration in gastric motility, and they concluded that the alteration of peristaltic activity might be an explanation for the relief of pain. The effect of vagus section on gastrointestinal motility was noted by other observers. ^{32, 38}

Brody and Quigley 34 observed that the systolic type of pressure wave was abolished after vagotomy, and that basal pressures in the body of the stomach were decreased by 0 to 3 cm. of water. Smith, Ruffin and Baylin 35 reported that the "acid test" was persistently negative in 11 patients after transthoracic vagotomy, whereas before the operation the test had resulted

in typical ulcer pain in every case.

Another tool useful in the investigation of this problem was afforded by the development of potent antonomic blocking agents.³⁶ Ulcer pain may be promptly relieved by parenteral administration of ganglionic blocking drugs.³⁷⁻⁴⁸ These agents afforded an opportunity for separating to some degree the several variables concerned with the mechanism of ulcer pain. The level of gastric acidity could be raised or lowered by adding or withdrawing hydrochloric acid from the stomach, and the motility of the stomach and duodenum could be altered by administration of these agents parenterally.

EXPERIMENTAL OBSERVATIONS

The experimental observations were carried out in five phases: (1) the effect of intragastric administration of HCl on ulcer pain; (2) fluoroscopic and roentgenographic observations with acid barium; ^{43, 44} (3) alterations in intraluminal pressures accompanying ulcer pain; ^{45, 46} (4) fluorocinematographic observations; ^{47, 48, 49} and (5) gastric acidity studies. ⁵⁰

THE EFFECT OF INTRAGASTRIC ADMINISTRATION OF HCL ON ULCER PAIN

The "acid test" was performed by instilling 200 ml. of 0.1 N HCl or 200 ml. of a suspension of barium sulfate in 0.1 N HCl into the stomachs of patients with active ulcers who had experienced pain within the previous 24 to 48 hours, or who were having spontaneous pain at the time of the study.⁴⁸⁻⁴⁶ A total of 155 studies was carried out on 131 patients. The development of typical ulcer pain or the continuation or accentuation of

spontaneous pain following instillation of acid into the stomach was considered to be a positive test. The test was considered to be negative if pain did not follow the introduction of hydrochloric acid into the stomach within 30 to 60 minutes, or if pain which had been present immediately prior to instillation of the acid ceased within a few minutes after administration of the acid (figure 1).

Spontaneous ulcer pain was present at the time of instillation of the hydrochloric acid in 42 of the studies. The response to the infused acid in this group of patients was as follows: The ulcer pain was relieved following instillation of acid in 18 patients, ulcer pain was increased in severity in seven patients, and the pain remained unchanged in 17 patients. One hundred thirteen patients had a history of ulcer pain within the previous 24 to 48 hours. Pain followed introduction of hydrochloric acid in 30 of these patients during the period of study, while in the remaining 83 patients no

EFFECT OF INTRAGASTRIC HCL ON ULCER PAIN TOTAL STUDIES SPONTANEOUS PAIN 42 PAIN WITHIN PREVIOUS 24-48 HOURS 113 NEGATIVE TESTS POSITIVE TESTS PAIN PAIN NO PAIN PAIN RELIEVED INDUCED INCREASED UNCHANGED PAIN 30 7 17 83 18 101 54 Fig. 1.

pain followed ingestion of hydrochloric acid. The time interval between introduction of acid and the development of pain varied between two and 30 minutes, with a mean value of 10 minutes. Fifty-four patients had positive tests, and 101 patients had negative tests.

In 121 of the 155 studies a single aliquot of 200 ml. of 0.1 N HCl to which a small amount of barium sulfate had been added, was given initially or followed the aliquot of 0.1 N HCl. Pain occurred during the study following instillation of acid-barium in 44 of the 121 studies (36%):

FLUOROSCOPIC AND ROENTGENOGRAPHIC OBSERVATIONS WITH ACID-BARIUM

In view of the discrepancies between the frequency of positive tests in our experience (approximately 36%) and the frequencies reported in the literature by some other investigators (approximately 85 to 90%), 4-8, 12, 13

a study of the motor activity of the stomach and the duodenum was undertaken by adding barium sulfate to the hydrochloric acid. The titratable acidity was not altered by adding barium sulfate.⁴⁴

In every instance, ulcer pain was associated with abnormal motility as demonstrated by roentgen study. This consisted of an abnormality of the antral evacuation mechanism. When pain ceased spontaneously, normal evacuation was resumed. The delay in gastric evacuation was accompanied by hypermotility of the stomach.⁴⁴

Ulcer pain was relatively constant in most patients, although in a few with gastric ulcers the pain was observed to be synchronous with waves of spasm in the vicinity of the ulcer. In five patients with pyloric channel ulcer the underlying pain increased in crescendo fashion simultaneously with peristaltic waves advancing toward an apparently closed pylorus. Pain ceased following cessation of these waves.

The pain subsided spontaneously during most of the studies when normal evacuation was resumed. The effect of cholinergic blocking agents (Banthine, Probanthine, Tricoloid and Piptal) was studied in 26 patients having a positive acid-barium test in whom the pain pattern was well established. Prompt and dramatic relief of ulcer pain followed parenteral administration of the blocking agents in 25 of the 26 studies. The relief of pain following administration of the cholinergic blocking agents was noted to be synchronous with the cessation of gastrointestinal motor activity. The length of time required for relief of pain varied from two to 30 minutes, with a mean value of nine minutes. The one patient who was not relieved by cholinergic blocking agents was found at operation to have a perforated, walled-off duodenal ulcer.

Detailed fluoroscopic observations were also carried out during the pain period of 16 of 17 positive studies concurrently with the intraluminal pressure measurements. These latter measurements are reported in more detail below. A delay in gastric evacuation, with apparent closure of the pylorus and absence of acid-barium at the ulcer site in the duodenum, was observed in 11 patients with duodenal ulcer. Ulcer pain ceased in these patients when the acid-barium was evacuated into the duodenum.

ALTERATIONS IN INTRALUMINAL PRESSURES ACCOMPANYING ULCER PAIN

The motor activity of the stomach and duodenum was recorded as pressure changes detected by Statham strain gauges and a Sanborn polyviso recorder employing three tandem fluid-filled catheters with their tips 5 cm. apart. ^{45, 46, 47} Intraluminal pressures from the three sites were recorded during a fasting control period varying between 30 and 70 minutes. A suspension of barium sulfate in 200 ml. of 0.1 N HCl was then instilled into the stomach through the proximal tube. Ulcer distress occurred in some patients spontaneously, and in others followed infusion of the acid-barium suspension.

Intraluminal pressures were recorded from the cardia, body and antrum of the stomach and the duodenum of 10 normal subjects, and of 62 patients with peptic ulcer, none of whom had evidence of pyloric obstruction. Twenty-nine patients had an active duodenal ulcer, 10 had an inactive duodenal ulcer, and 13 had a gastric ulcer. Fifty-six tracings were available for detailed quantitative analysis.

Analysis of the tracings revealed that division of wave types was not possible on the basis of amplitude.^{51, 52} The waves were divisible into two groups, based upon duration. Waves of less than 30 seconds' duration were

MOTOR RESPONSE TO HYDROCHLORIC ACID

CONTROL PERIOD VS. EVACUATION PERIOD

(Paired Comparison)

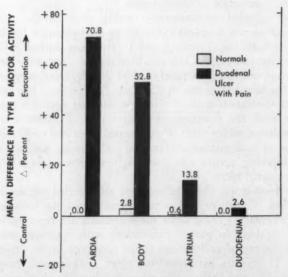


Fig. 2. Changes in gastroduodenal intraluminal pressure wave activity (Type B), expressed as differences in mean percentage of observed time for normal and for active duodenal ulcer group—paired comparison between control and evacuation periods. (Reprinted by permission from Gastroenterology 32: 1025, 1957.)

termed Type A, and those of more than 30 seconds' duration were termed Type B. No quantitative differences in the intraluminal pressure waves were observed between normal subjects, patients without ulcer distress, and those with ulcer distress.

A quantitative estimate of gastrointestinal motor activity was obtained by dividing the sum of the duration of the phasic and tonic waves secondary to gastrointestinal motor activity by the total period of observation.^{58, 54} The period during which activity of a given type was present could then be expressed as a percentage of time. Differences between differing periods or groups were expressed as Δ per cent. The total period of observation, duration of the control, evacuation, inhibition, and pain periods were measured separately. The mean values and the standard deviation for each wave type for total activity were calculated for each level studied. Paired comparisons were made between the following categories: (1) control period activity and evacuation period activity, and (2) control period activity and pain period activity for patients with peptic ulcer. Unpaired comparisons by the method of pooled variance were made between the following categories: (1) normals and patients with duodenal ulcer; (2) normals and patients with gastric ulcer; (3) patients with active ulcer and with inactive ulcer, and (4) ricer patients with pain and without pain.

No statistical difference between control period activity and evacuation period activity was observed in the normal subjects. Peristaltic waves advancing toward the apparently closed pylorus, as observed fluoroscopically, revealed a fair correlation with Type A waves of high amplitude. Peristaltic waves advancing toward an apparently open pylorus resulted in Type A waves of low amplitude, or were unaccompanied by significant change in intraluminal pressure. An excellent correlation was demonstrated between

MOTOR ACTIVITY IN ACTIVE DUODENAL ULCER

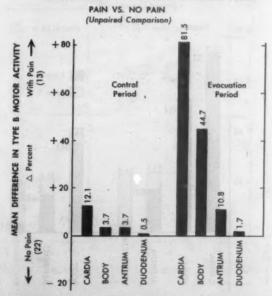


Fig. 3. Differences in gastroduodenal intraluminal pressure wave activity for control and evacuation periods—unpaired comparison between group with active duodenal ulcer without pain and group with active duodenal ulcer with pain. (Reprinted by permission from Gastroenterology 32: 1025, 1957.)

prolonged, nonpropulsive segmental contractions observed during the early phase of evacuation, and Type B waves.

Little difference was observed in gastroduodenal pressure wave activity during the control period between normal subjects and patients with active duodenal ulcer. A statistically significant increase in Type B activity was observed during the evacuation period of 29 patients with active duodenal ulcer, regardless of the presence or absence of ulcer pain. These differences were as follows: Δ 12.9% for the body of the stomach, Δ 7.1% for the antrum of the stomach. Total duodenal activity was increased during the evacuation period by Δ 4.3% in patients with active duodenal ulcers.

A significantly greater increase in Type B activity occurred during the evacuation period in patients with duodenal ulcer who experienced pain as compared with the normal subjects (figure 2). These differences were as follows: cardia of the stomach, Δ 70.8%; body of the stomach, Δ 52.8%; antrum of the stomach, Δ 13.8%; duodenum, Δ 2.6%. In contrast, the pain-free subgroup of duodenal ulcer patients revealed little change in activity during evacuation of the acid-barium suspension (figure 3).

Paired comparisons were made between control-period intraluminal pres-

MOTOR RESPONSE DURING PAIN

CONTROL PERIOD VS. EVACUATION PERIOD

(Paired Comparison)

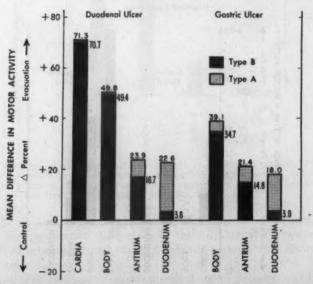


Fig. 4. Motor responses during pain as measured by changes in gastroduodenal intraluminal pressure wave activity, expressed as differences in mean percentage of observed time for duodenal and gastric ulcer subjects—paired comparison between control and evacuation (after instilling acid-barium) period.

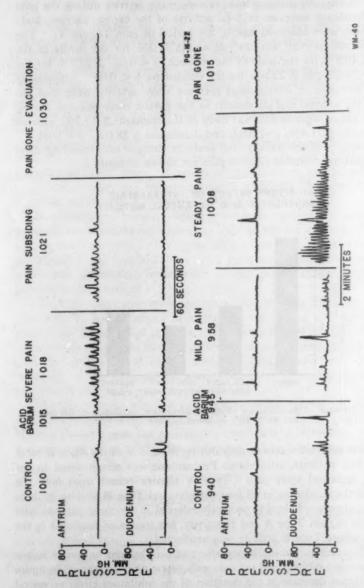


Fig. 5. Intraluminal pressure response to pain. Upper tracing: A 45 year old man with a chronic duodenal ulcer experienced severe pain after instillation of acid-barium accompanied by Type A and B activity in both antrum and duodenum, but predominantly in the antrum. Lower tracing: A 57 year old woman with a chronic duodenal ulcer experienced pain after instillation of acid-barium accompanied by marked increase in Type A and lower amplitude Type B waves in the duodenum.

sure wave activity and intraluminal pressure wave activity during the pain period. Significant increases in total activity of the cardia, antrum, body and duodenum were observed during the period of pain (figure 4). The increases in total activity were as follows: Δ 71.3% for the cardia of the stomach, Δ 49.8% for the body of the stomach, p < 0.02, Δ 23.9% for the antrum, p < 0.05, and Δ 22.6% for the duodenum, p < 0.05. Statistically significant increases in intraluminal pressure wave activity were also observed for the antrum and duodenum in the gastric ulcer patients during pain. The values were as follows: body of the stomach, Δ 39.1%, antrum of the stomach, Δ 21.4%, p < 0.02, and duodenum Δ 18.0%, p < 0.05.

Two examples of the intraluminal pressure changes accompanying ulcer pain and following cessation of ulcer pain are shown in figure 5.

INHIBITORY EFFECT OF INTRAGASTRIC HYDROCHLORIC ACID ON ANTRAL MOTILITY

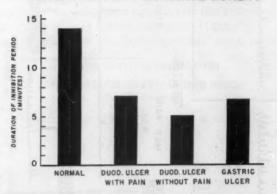


Fig. 6. Duration of the inhibitory effects of intragastric instillation of 200 ml. of 0.1 N HCl on antral motility.

Ulcer pain subsided spontaneously during the course of the study in most cases. In four patients, intravenous Probanthine was administered to patients with sustained ulcer pain. Type A activity ceased from both the stomach and the duodenum in all four patients, and Type B activity in three of the four patients. Pain was promptly relieved in the three patients who had cessation of both Type A and B activity, but continued unabated in the one patient whose Type B activity was unaffected.

The differences in the inhibitory effect of acid-barium on antral motor activity of normal subjects and patients with peptic ulcer are shown in figure 6. A significant decrease in the duration of the inhibitory effect on antral motility was observed whether the patients had an active or an inactive ulcer, and whether or not they subsequently experienced ulcer pain during the course of the study.

FLUOROCINEMATOGRAPHIC OBSERVATIONS

Formerly, intermittent fluoroscopy and spot x-ray films were the only roentgen technics available for correlating the intraluminal pressure changes with gastrointestinal motility. The development of a fluorocinematographic apparatus with low roentgen output (1 to 3 roentgens per minute at the tabletop) has permitted objective study of gastrointestinal motor activity over a more prolonged period of time.⁴⁷ Superimposition of the intraluminal pressure tracings on the cine film permits exact correlation of the pressure and motility data.

Fluorocinematographic studies have been carried out during evacuation of barium-sulfate or acid-barium in normal subjects, and in 24 patients with a history of peptic ulcer. Nineteen of these patients had an active gastric or duodenal ulcer, and the remaining five patients had been subjected to a gastric resection or a vagotomy and gastroenterostomy.

Observations on normal subjects revealed that gastric evacuation proceeds as peristaltic waves sweep from the region of the incisura over the antrum, pylorus and duodenum. The segmenting waves were seen at a rate of three per minute in the normal subjects. A good correlation between evacuation waves and segmenting contractions of the gastric antrum was observed, as reported by Smith et al. 55

The fluorocinematographic studies of ulcer patients who were not having pain revealed no alterations in motor activity. Combined fluorocinematographic and intraluminal pressure studies were carried out following administration of acid-barium in three patients with active ulcer, one of whom had pain during the period of the study. Antral hyperactivity and delayed emptying of the stomach were observed in this patient, confirming the previous intraluminal pressure observations.

The five patients who had had removal of the antrum and pylorus or a gastroenterostomy demonstrated rapid emptying of the gastric remnant. None of these patients had pain during the course of the study. Evacuation was unaccompanied by significant changes in intraluminal pressure.

GASTRIC ACIDITY STUDIES

Gastric acidity levels were measured in 25 patients during the acid test. The mean value for HCl initially was 23 mEq./L. This value rose to 68.8 mEq./L. following infusion of 200 ml. of 0.1 N HCl. After instillation of 200 ml. of acid-barium suspension, the mean values were 71.4 mEq./L. No differences were observed between the initial acid values of patients having spontaneous pain and those having no pain. However, the acid values were higher at 30 minutes after instillation of acid-barium in patients who had had pain.

Acidity was also measured concurrently with the intraluminal pressure studies. The concentration of free acid in patients without pain was 26.3

mEq./L. initially, 23.8 mEq./L. at the end of the control period, and 57.5 mEq./L. 30 minutes after instillation of acid-barium (figure 7). In contrast, the mean values of patients with pain were 0.4 mEq./L. at the beginning of the control period, 18.4 mEq./L. at the end of the control period, and 77.2 mEq./L. 30 minutes after instillation of acid-barium. The acid values were approximately equal in both the pain and the pain-free groups initially. The higher acid values noted 30 minutes after instillation of acid-barium in the pain group were interpreted as being indicative of delayed evacuation of the instilled acid.

Although some investigators have reported that gastric acidity is normal in patients with uncomplicated duodenal ulcer,⁵⁶ studies of the one-hour basal gastric secretion in 220 patients indicated that the secretory rate in patients with duodenal ulcer was usually two to three times that of the normals.^{57, 58}

GASTRIC ACIDITY DURING INTRALUMINAL PRESSURE WAVE STUDIES

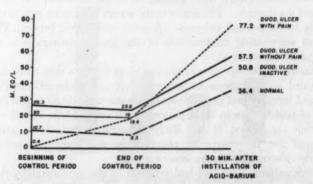


Fig. 7. Gastric acidity in mEq./L. during intraluminal pressure studies. Two hundred milliliters of acid-barium were instilled at the end of the control period.

The secretory rates in gastric ulcer patients were not higher than normal. No significant differences in secretory rates were observed in patients with active duodenal ulcer (mean, 85.6 mg./hour) as compared to patients with inactive duodenal ulcer (mean, 80.3 mg./hour), confirming previous observations. ^{14, 56, 59, 60, 61} It has been shown that maximal acid secretion is proportional to the parietal cell mass, ⁶² which does not change during remission or exacerbation.

DISCUSSION

Ulcer pain cannot be studied without considering the factors underlying the pathophysiology of the digestive tract pain in general. Some of these can be studied directly, but others can be arrived at only by inferential observations.⁶³ Particular problems are posed for the student of ulcer pain.

Despite the development of objective technics to record the physiologic phenomena accompanying ulcer distress, the investigator is still dependent upon subjective observations of the patient regarding the onset, duration, character and severity of the ulcer distress. Further, the use of objective technics necessitates study of the patient in an experimental situation, which differs markedly from that in which he usually experiences ulcer pain.

Despite these limitations, certain facts have emerged from the foregoing observations which can be correlated with our knowledge of the motor and secretory physiology of the ulcer patient: (1) No significant differences in motor activity as measured by intraluminal pressure recording were observed during the control period (before instilling hydrochloric acid) between normal individuals, pain-free ulcer patients, and patients who subsequently developed ulcer pain. (2) Statistically significant increases in intraluminal pressure wave activity of the cardia, body, and antrum of the stomach, and the duodenum were observed following instillation of 0.1 N HCl in patients who developed ulcer pain. (3) This increase in intraluminal pressure wave activity was correlated with fluoroscopic or fluorocinematographic evidence of gastrointestinal motor activity. Intraluminal pressure wave activity of less than 30 seconds' duration (Type A) correlated with phasic evacuation wave activity of the stomach. Intraluminal pressure wave activity of more than 30 seconds' duration (Type B) correlated with changes in tonus or size of the organ. (4) The increases in phasic and tonic intraluminal pressure wave activity were not accompanied by an increased rate of gastric evacuation in patients with peptic ulcer. (5) Instillation of 0.1 N HCl resulted in a decreased period of inhibition of antral evacuation motor activity in patients with peptic ulcer, regardless of whether they were in an active or inactive phase, as compared with the normal individuals.

The rate of gastric evacuation depends upon three variables: (1) the propulsive activity of the stomach; (2) the effectiveness of the inhibitory mechanisms which normally check emptying of the stomach, ⁶⁴, ⁶⁵ and (3) the nature of the gastric contents. The decrease in the inhibitory effect of instilled acid on antral motor activity of ulcer patients may result from a derangement of function of the neural receptors on the gastric or duodenal side of the pylorus, ⁶⁴ or as a result of failure of secretion of enterogastrone.

The secretion of acid depends upon stimulation of receptors, mediated by either neural or hormonal mechanisms, which excite the secretory cells. 66 Maximal secretory capacity has been correlated with both the duration of ulcer symptoms and the size of the parietal cell mass. Whether this represents a "work hyperplasia" of the parietal cells has not yet been clarified. It has also been postulated that gastric hypersecretion in patients with duodenal ulcers may result from the failure of the duodenal inhibitory mechanisms which normally slow gastric secretion as the gastric contents become more acid. 67 The addition of 200 mEq. of HCl per liter depressed secretion of acid by about one fifth in normal subjects, but it did not suppress secretion

of acid in patients with duodenal ulcers.⁶⁸ The acidity curve following instillation of hydrochloric acid has been used as an aid in the diagnosis of duodenal ulcer.⁶⁹

Shay, 67 in addition to implicating failure of the duodenal inhibitory mechanisms on the secretion of acid in patients with duodenal ulcer, postulated that the threshold of the mechanism which delays gastric evacuation was raised during activity of the ulcer, and returned to normal during periods of remission. The present data indicate that failure of normal function of the duodenal regulatory mechanism is an important part of the pathophysiology of the ulcer patient, regardless of the activity of the ulcer.

These observations have an important relationship to the mechanism of pain in patients with duodenal ulcer. Such patients have an increased number of parietal cells, as a result either of hereditary influences or of "work hyperplasia." These cells are capable of secreting a larger amount of hydrochloric acid than is normally present. Although the increased amount of acid may act as a stimulus for ulcer pain, the data indicate that ulcer pain is not the result of direct chemical irritation by hydrochloric acid, but of abnormal motor activity. Engorgement of the mucosa may result in lowering the threshold to acid, as the acid values do not differ in the active and inactive phases. Further, the increased amount of acid secreted does not effectively inhibit either further secretion of acid or antral evacuation motor activity. The gastric contents are not delayed from entering the duodenum until the intragastric pH rises above the critical level.⁷⁰

Studies on fistulous subjects have indicated that hypermotility and increased vascularity accompany hypersecretion. 71, 72 The increased vascularity of the mucosa lowers the threshold to noxious stimuli. 63 However, the mechanism responsible for the development of ulcer pain is similar to that of pain arising from other hollow viscera, namely, disordered motor activity. This consists of increased antral motor activity which does not result in more rapid gastric evacuation. Rather, this increased antral activity is accompanied by apparent closure of the pylorus. When opening of the pylorus takes place and gastric evacuation proceeds, the pain subsides.

The normal functions of the pyloric sphincter and the factors regulating these activities have not been clearly worked out. Quigley ^{24–28, 34} felt that the major function of the pylorus was to prevent regurgitation from the duodenum into the stomach following evacuation activity of the antral pumping mechanism. Others, ⁷⁸ while acknowledging the presence of a sphincter anatomically, have not been able to document the physiologic phenomena which should normally accompany such a structure. However, more recent studies indicate that a zone of increased pressure is present in the region of the pyloric sphincter, and that this pressure may be markedly exaggerated in patients with apparent spasm of the pylorus or ulceration in the vicinity of the pyloric channel. ⁷⁴ Hydrochloric acid has been demonstrated to be a potent stimulus to the production of spasm in other portions of the gastro-intestinal tract, and the data suggest that a similar response takes place in

the ulcer patient during the period of ulcer pain, resulting in dyssynergia of the pylorus, and uncoördinated motor activity.

The pathophysiologic mechanisms responsible for ulcer pain in patients with gastric ulcer are less easy to explain. The gastric secretory rate in patients with gastric ulcer is usually within the normal range or lower. Further, the increases in intraluminal pressure wave activity accompanying ulcer pain, while statistically significant, are not so striking as those accompanying duodenal ulcer. On occasion, in patients with large gastric ulcers, localized spasms have been correlated with ulcer pain.

Many gastric ulcers reach a large size before becoming symptomatic. When pain occurs in gastric ulcer, it is frequently of somatic origin. At autopsy, the incidence of gastric and of duodenal ulcer is similar, suggesting that many gastric ulcers are entirely asymptomatic during the lifetime of the patient.⁷⁸

What, then, is the explanation for the relief of pain following ingestion of milk, cream or other substances? Christensen 14 found that gastric motility was most effectively inhibited by the egg-milk diet, and that the gastrographic waves were smaller during gastric evacuation than during hunger contractions. It would appear that Quigley's supposition is correct, namely, that there is a subtle but important difference between evacuation and resting motor activity. The relief of pain appears to be related to the conversion of resting to evacuation motor activity following ingestion of food. Relief following administration of cholinergic blocking agents has been correlated with cessation of gastrointestinal motor activity.

A variety of ingested substances may temporarily relieve ulcer pain. In normal subjects, ingestion of these substances results in inhibition of antral motor activity to a variable degree. Antral motor activity continues unabated or is increased following ingestion of these substances in patients with active duodenal ulcer. Doret 76 has suggested that either the diseased duodenum of the ulcer patient is adjusted to the unfavorable chyme, or that the reflex mechanisms are defective, and evacuation proceeds in spite of the more acidic nature of the gastric contents. These observations will require further study.

SUMMARY

The mechanism of ulcer pain was studied using the following approaches: (1) study of the effect of intragastric administration of 200 ml. of 0.1 N HCl on ulcer pain; (2) study of the fluoroscopic and roentgen alterations following acid-barium administration; (3) measurement of intraluminal pressures from the stomach and duodenum in normal subjects, in patients without ulcer pain, and in patients with ulcer pain; (4) correlation of the intraluminal pressure changes with the fluorocinematographic (GE-TVX) appearance of the stomach and duodenum; and (5) study of basal gastric secretion and gastric acidity during ulcer pain.

Intragastric administration of 200 ml. of 0.1 N HCl or acid-barium was followed by continuation of spontaneous pain or induction of ulcer pain in

54 of 155 studies. The gastric acidity was measured initially, prior to instilling HCl, 30 minutes after HCl administration, and 30 minutes after administration of acid-barium. The initial acid values did not differ, although the same amount of instilled acid resulted in higher acid values 30 minutes later in patients who developed ulcer pain, suggesting delayed evacuation of the instilled acid in this group.

Ulcer pain was accompanied by a significant increase in motility, as measured by intraluminal pressure wave activity synchronous with the duration of the ulcer pain. The increases were as follows: cardia of the stomach, Δ 71.3%; body of the stomach, Δ 49.8%, p < 0.02; gastric antrum, Δ 23.9%, p < 0.05; and duodenum, Δ 22.6%, p < 0.05. The inhibitory effect of intragastric instillation of hydrochloric acid on antral motility was reduced for patients with duodenal ulcer to 5.6 \pm 8.7 minutes, as compared to the normal period of 14.0 \pm 10.9 minutes.

A significant delay in gastric evacuation accompanied ulcer pain, despite the hypermotility of the antrum. These findings were interpreted as indicative of dyssynergia of antral-pyloroduodenal evacuation mechanism as the result of increased resistance at the pyloric sphincter.

Relief of pain occurred spontaneously in most instances with resumption of evacuation activity. Relief of pain following ingestion of food appears to be related to the conversion of resting to evacuation motor activity. Relief of pain following vagotomy and cholinergic blocking agents was related to their inhibitory effect upon gastrointestinal motor activity.

The data do not support the concept that ulcer pain is produced by direct chemical irritation by hydrochloric acid. The mucosal engorgement accompanying the ulcer may lower the threshold to hydrochloric acid, permitting the acid and perhaps other stimuli to initiate the reflex disturbance in the motor activity of the stomach and duodenum which appears to be the direct cause of ulcer pain.

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SUMMARIO IN INTERLINGUA

In le curso del passate septe annos, observationes esseva facite in plus que 500 patientes con respecto al mechanismo del dolor de ulcere. Le sequente methodos esseva usate: (1) Le studio del effecto de administrationes intragastric de 200 ml de acido hydrochloric de 0,1 N; (2) le studio del alterationes fluoroscopic e roentgenographic post administrationes de acido e barium; (3) le mesuration del pression intraluminal de stomacho e duodeno in normal subjectos de controlo e in patientes de ulcere con e sin dolor; (4) le correlation del alterationes del pression intraluminal con le apparentia fluorocinematographic (GE-TVX) del stomacho e del duodeno; e (5)

le studio del basal secretion gastric e del aciditate gastric durante le presentia de dolores de ulcere.

Le administration intragastric de 200 ml de acido hydrochloric de 0,1 N o de acido e barium esseva sequite per le continuation de dolores spontanee o per le induction de dolores in 54 inter 155 studios. Le aciditate gastric esseva mesurate initialmente, ante le instillation de acido hydrochloric, 30 minutas post le administration de acido hydrochloric, e 30 minutas post le administration de acido e barium. Le valores initial pro acido non differeva inter le patientes in qui le experimento evocava dolores e le patientes in qui isto non esseva le caso, sed le mesme quantitate de acido instillate resultava post 30 minutas in plus alte valores pro le acido gastric in le patientes qui subsequentemente disveloppava dolores de ulcere. Isto pare indicar un retardo del evacuation del instillate acido in iste ultime gruppo de patientes.

Dolores de ulcere esseva accompaniate de un significative augmento del motilitate gastro-duodenal, a judicar per mesurationes del activitate de undas de pression intraluminal. Iste augmento de motilitate esseva synchronic con le dolor de ulcere. Le augmentos de motilitate, mesurate per le activitate de undas de pression intraluminal esseva le sequentes: Cardia del stomacho, 71,3%; corpore del stomacho, 49,8% (valor de p: minus que 0,02); antro gastric, 23,9% (valor de p: minus que 0,05); e duodeno, 22,6% (valor de p: minus que 0,05). Le effecto inhibitori del instillation de acido hydrochloric de 0,1 N super le motilitate del antro esseva reducite in patientes con ulcere duodenal a $5,6 \pm 8,7$ minutas, in comparation con un valor normal de 14,0 \pm 10,9 minutas.

Un retardo significative in le evacuation gastric accompaniava le dolores de ulcere, in despecto del hypermotilitate del antro. Iste constatationes esseva interpretate como indicante un dyssynergia in le mechanismo de evacuation antro-pyloro-duodenal como resultato de un augmento del resistentia del sphinctere pyloric.

In le majoritate del casos, le alleviamento del dolores coincideva con le resumption del activitate de evacuation. Le alleviamento del dolores post le ingestion de nutrimento pareva esser relationate al conversion del activitate motori ab le stato de reposo al stato evacuatori. Le alleviamento del dolores post vagotomia o post le administration de cholinergic agentes de blocage esseva relationate con le effecto inhibitori que ille mesuras exerceva super le activitate motori gastrointestinal.

Le datos non supporta le conception que le dolores de ulcere es causate per le directe irritation chimic de acido hydrochloric. Le congestion mucosal que accompania ulceres active reduce possibilemente le limine pro noxie stimulos. Le mechanismo responsabile pro le disveloppamento de dolores de ulcere es simile a illo del dolores que es occasionate per visceres sin contento. In ambe casos il se tracta de un disordine in le activitate motori.

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EVALUATION OF APPETITE SUPPRESSANTS*

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The high incidence of obesity in our population presents a definite public health problem. It is estimated that approximately 20 million people in the United States are clinically obese, and that 5 million of these weigh at least 20% above the optimum. The magnitude of the problem is presented in the insurance statistics, which clearly define the increased mortality rates for overweight individuals, especially those beyond the age of 45. Obesity is associated with increased susceptibility to cardiovascular disease, diabetes and gall-bladder disease, and of course represents an additional risk in surgery.¹

Although there are recognized hereditary, constitutional and hormonal factors contributing to excess weight, overeating is without a doubt the greatest single causative factor in obesity. The problem is one of balance between food intake and energy expenditure. From a practical point of view, therefore, the chief method of weight control is control of the caloric intake.

The methods of controlling food intake are numerous. Bulk laxatives have been used to fill the stomach and dull the appetite. Certain fad diets, by virtue of their extreme monotony, tend to limit food intake without regard for caloric content of the food. Another technic, utilizing frequent small feedings of foods having low caloric value, is widely used since it tends to prevent hunger and thus helps to keep the individual more or less cooperative. Low fat, low carbohydrate and low protein diets are all modifications of this approach. Obviously, such diets are too restrictive, since their prolonged use could result in nutritional deficiencies. The optimal method of limiting food intake is to modify the appetite. In this way, caloric intake is controlled, yet the diet as a whole is satisfactory from the standpoint of food value. It is in this latter approach that the anorexigenic drugs are most valuable aids in the successful treatment of obesity.

Psychologic factors may contribute greatly to obesity, in the form of neurotic overeating. Irritability, boredom, anxiety and emotional tension are frequently found to be the basis for nonphysiologic hunger. It seems reasonable, therefore, to attempt treatment of neurotic overeating with a combination of an effective appetite suppressant and a calmative agent. Some degree of mood elevation is provided by amphetamine, and this is an important aspect of therapy for some patients. The resulting increase in ambition and the feeling of well-being help the patient to adjust his eating

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habits, and may enable him to cope with some of the underlying causes of his obesity.

The more important chemical agents now employed as anorectic drugs are the sympathomimetic amines, such as amphetamine (1-phenyl-2-amino propane), methamphetamine, phenylpropanolamine and phenmetrazine. Some of the earlier comparative studies 2, 8, 4 have shown that dextroamphetamine was the most effective anorexigenic compound. Later studies 5, 6 have demonstrated that a 3-to-1 ratio of dextro to racemic amphetamine produced better and smoother appetite suppression than did dextro-amphetamine alone. More recently, published reports on the effectiveness and low toxicity of new anorectic agents, amphetamine alginate and phenmetrazine,7,8,9 have aroused considerable interest.

The purpose of this paper is to report the data obtained in a comparative clinical evaluation of a number of currently available anorexigenic drugs and some new experimental preparations. The latter include two combinations of amphetamine with calmative agents and a newly synthesized. non-amphetamine preparation, 2-phenyl-tert.-butylamine.

Two distinct and separate groups of patients were used. The larger group was composed of hotel employees * working in office, kitchen, laundry and housekeeping; the smaller group, of institutional patients.† All patients were volunteers with weight problems of varying duration. In general, those of the office group were less overweight, but were more occupied and disturbed by their small amount of excessive weight. A few were of the clear-cut Fröhlich type. In the case of patients with hypertension or previous coronary disease, where the use of stimulants might be considered to be unwise, frequent laboratory and clinical examinations were conducted to provide adequate supervision of the patient. Most of the subjects were patients whose excess weight was a real problem and its loss important. No recommendation was made with respect to diet. In a few instances where consumption of alcohol was a problem, moderation was advised.

DESIGN OF STUDY

Patients were given a seven-day supply of the medication by the nurse in charge. Medications were distributed in boxes of appropriate size, with the code number and directions thereon. Observations as to weight, sideeffects and blood pressure were taken each time the patient returned for an additional supply of medication.

Ten different coded medications and a placebo were included in the study. The available drugs were purchased on the open market and administered as recommended by the manufacturer. These, as well as the experimental preparations,‡ were under a code designation. Each of the medications

^{*} Hotel Statler, Boston, Massachusetts. † Long Island Hospital, Boston, Massachusetts.

The R. J. Strasenburgh Company, of Rochester, N. Y., supplied these preparations.

was administered to a separate group of approximately 25 patients. The patients were selected and assigned to a particular medication in rotation. The study was conducted over an eight-week period. The use of coded preparations made it possible to conduct the study on a completely blind basis insofar as the patient and the observer were concerned, although the medications were not identical in appearance. An observation card was designed to facilitate the recording of weight, blood pressure, mood change, and other side-effects.

The data were compiled and recorded, and a preliminary analysis was made prior to the decoding of the medications.

The composition of the coded preparations and their dosage schedules were as follows:

| Code | Composition | Dosage Schedule |
|------|--|-------------------------|
| 1-S | Placebo | T.I.D. |
| 2-S | d-amphetamine SO ₄ , 5 mg. | T.I.D. |
| 3-S | phenmetrazine, 25 mg. | T.I.D. |
| 4-S | d-amphetamine SO ₄ , coated granules, 15 mg. | One capsule upon rising |
| 5-S | d- and dl-amphetamine as resin complexes, 12.5 mg. | One capsule upon rising |
| 6-S | d- and dl-amphetamine as resin complexes, 20 mg. | One capsule upon rising |
| 7-S | d- and dl-amphetamine, 20 mg., and benactyzine, 16 mg., as resin complexes | One capsule upon rising |
| 7-SS | d- and dl-amphetamine, 12.5 mg., and benactyzine, 16 mg., as resin complexes | One capsule upon rising |
| 8-S | d- and dl-amphetamine, 20 mg., and methyl-orthotolyl-quinazolone, 40 mg., as resin complexes | One capsule upon rising |
| 9-S | 2-phenyl-tertbutylamine, 30 mg., as resin complex | One capsule upon rising |
| 10-S | d- and dl-amphetamine, 20 mg., and methyl-orthotolyl-quinazolone, 5 mg., as resin complexes | One capsule upon rising |
| | | |

It was difficult to maintain the size of the original group throughout the clinical study. However, keen interest in the problem produced a loyal group. Medications were rotated in turn as new patients came under study. As soon as 25 patients were on any one medication, no further subjects were added, although toward the end of the study so many patients wished to participate that the size of certain groups was enlarged. Some of the subjects dropped out of the study either because of dissatisfaction or because of excessive side-effects.

Initially, nine unknowns were used coded, 1-S to 9-S. However, the side-effects obtained with medication 7-S were excessive, and as a result the dose of amphetamine was reduced from 20 mg. to 12.5 mg., and the latter dosage was coded 7-SS. In view of the fact that two preparations (Code

8-S and 9-S) were new and experimental, appropriate laboratory studies, periodic blood counts and urinalyses were carried out on these groups. At the conclusion of the study the data were tabulated, and are summarized in tables 1 through 4.

In general, there seemed to be a high correlation of weight loss with the incidence of side-effects for the amphetamine drugs. For example, the 20 mg. d- and dl-amphetamine as resin complexes produced the most effective weight loss in the amphetamine category, yet for some patients a single morning dose of this size resulted in hyperactivity late at night and insomnia. Although cross-over methods of evaluation were not incorporated in this study, it was independently observed that some patients who had reached a plateau in their weight reduction with a given amphetamine preparation

Table 1
Tabulation of Weight Loss Data

| Code | No. | S | ex | Av. Initial | Tot. | | Av | erage Wei | ght Loss | per Pat | ient per I | Day (lbs.) | |
|-------------|-----------|----|----|-------------------|--------------------|------------|------------|------------|------------|------------|------------|------------|------------|
| No. | of Pt. | M | F | Pt. Wt. (lbs.) | No. of Pt. Days | 1st Wk. | 2nd Wk. | 3rd Wk. | 4th Wk. | 5th Wk. | 6th Wk. | 7th Wk. | 8th Wk. |
| 1-S | 26 | 10 | 16 | 164.0 | 693 | .058 | .042 | +.045 | +.045 | .071 | +.023 | C | |
| 2-5 | 23 | 5 | 18 | 170.9 | 1008 | .366 | .147 | .214 | .193 | .166 | .115 | +.062 | .05 |
| 3-S | 25 | 10 | 15 | 168.9 | 840 | .206 | .299 | .253 | .219 | .184 | .043 | .029 | +.020 |
| 4-5 | 22 | 9 | 13 | 165.8 | 714 | .313 | .414 | .116 | .227 | .187 | +.064 | +.055 | .117 |
| 5-S | 24 | 4 | 20 | 196.7 | 1015 | .159 | .214 | .169 | .247 | .101 | .092 | .184 | +.014 |
| 6-S | 22 | 11 | 11 | 166.6 | 826 | .425 | .259 | .338 | .200 | .189 | .190 | .090 | - |
| 7-S | 14 | 7 | 7 | 177.2 | 476 | .413 | .367 | .269 | .404 | .353 | .250 | .090 | .057 |
| 7-SS | 10 | 5 | 5 | 174.5 | 469 | .213 | .084 | .210 | .327 | .304 | .330 | .184 | .214 |
| 8-S | 32 | 14 | 18 | 170.9 | 1533 | .285 | .268 | .192 | .276 | .251 | .179 | .083 | .086 |
| 9-S | 29 | 10 | 19 | 170.9 | 1358 | .387 | .305 | .183 | .234 | .198 | .213 | .143 | .133 |
| 10-S | 20 | 0 | 20 | 163.7 | 861 | .391 | .088 | .071 | .149 | .089 | +.037 | .179 | .180 |

continued to lose weight when medication with a higher amphetamine content was prescribed.

From our present data it appears that the most effective weight loss occurs during the first six weeks of therapy with sustained-release amphetamine preparations. With the addition of benactyzine or methyl-orthotolyl-quinazolone * to the amphetamine, weight reduction continued at a significant level for several weeks longer than that obtained with amphetamine alone. Benactyzine, however, markedly increased the incidence of side-effects, whereas methyl-orthotolyl-quinazolone substantially reduced the side-effects produced by amphetamine. It is significant also that the size of the experimental groups receiving the latter preparation and of the group receiving 2-phenyl-tert.-butylamine remained essentially intact for the duration of this study. The non-amphetamine drug, 2-phenyl-tert.-butylamine, as a resin complex, produced a more satisfactory weight loss for a longer period of time when compared with the other medications. The incidence

^{*} Tuazole.

TABLE 2 Summary of Weight Loss Data

| Code | Medication | Tot. No. Pt. Days | Tot. Wt. Loss (lbs.) | Av. Wt. Lost per Pt. per Day (lbs.) |
|------|--|----------------------|-------------------------|---|
| 1-S | Placebo | 693 | 7.9 | 0.011 |
| 2-S | d-amphet. SO ₄ , 5 mg. | 1008 | 176.2 | 0.175 |
| 3-S | phenmetrazine, 25 mg. | 840 | 156.5 | 0.186 |
| 4-S | d-amphet. SO ₄ as coated granules, | 714 | 164.5 | 0.230 |
| 5-S | d- and dl-amphet. as resin complexes, | 1015 | 162.5 | 0.160 |
| 6-S | d- and dl-amphet. as resin complexes, 20 mg. | 826 | 206.7 | 0.252 |
| 7-S | d- and dl-amphet., 20 mg., + Benactyzine, 16 mg., as resin complexes | 476 | 152.7 | 0.321 |
| 7-SS | d- and dl-amphet., 12.5 mg., + Benactyzine, 16 mg., as resin complexes | 469 | 111.1 | 0.237 |
| 8-S | d- and dl-amphet. as resin complexes, 20 mg., + Tuazole, 40 mg. | 1533 | 337.5 | 0.220 |
| 9-S | 2-phenyl-tertbutylamine resin, 30 mg. | 1358 | 318.7 | 0.235 |
| 10-S | d- and dl-amphet. as resin complexes, 20 mg., + Tuazole, 5 mg. | 861 | 120.0 | 0.139 |

TABLE 3 Summary of Effect on Mood

| | Per Cent of Times Reported | | | | | | | |
|---|----------------------------|----------------------|----------------------|-------------------------|---------------------|--|--|--|
| Medication | No Change | Slightly Improved | Happy and Content | Slightly Hyperactive | Over- stimulated | | | |
| Placebo | 81 | 16 | 3 | 0 | 0 | | | |
| d-amphet. SO ₄ , 5 mg. | 31 | 32 | 21 | 15 | 1 | | | |
| phenmetrazine, 25 mg. | 33 . | . 32 | 31 | 4 | 0 | | | |
| d-amphet. SO ₄ as coated granules, 15 mg. | 23 | 16 | 41 | 19 | 2 | | | |
| d- and dl-amphet. as resin complexes, 12.5 mg. | 27 | 22 | 33 | 15 | 3 | | | |
| d- and dl-amphet. as resin | 19 | 28 | 31 | 10 | 5 | | | |
| complexes, 20 mg. d- and dl-amphet., 20 mg., + Benactyzine, 16 mg., as resin complexes | 19 | 18 | 34 | 24 | 5 | | | |
| d- and dl-amphet., 12.5 mg., + Benactyzine, 16 mg., as resin complexes | 20 | 25 | 22 | 29 | . 5 | | | |
| d- and dl-amphet. as resin complexes, 20 mg., + Tuazole, 40 mg. | 35 | 24 | 27 | 12 | 2 | | | |
| 2-phenyl-tertbutylamine resin, 30 mg. | 54 | 60 | 59 | 16 | 2 | | | |
| l- and dl-amphet. as resin complexes, 20 mg., + Tuazole, 5 mg. | 33 | 61 | 5 | 0 | 0 | | | |

TABLE 4
Summary of Side-Effects

| | | | | | Per | Per Cent of Times Reported | mes Repor | per | | | | |
|--|--------|-----------|------------------|-----------|-----|----------------------------|-----------|---------------------|--------|-----------------|-------------------|-------|
| Medication | Drowsy | Irritable | Hyper- active | Sleepless | Dry | Gritty | Vertigo | Slightly Jittery | Nausea | Refused Med. | Consti- pation | Other |
| Placebo | 10 | 1 | 15 | 0 | 1 | 0 | 0 | 0 | 2 | 0 | 2 | 1 |
| d-amphet. SO4, 5 mg. | 2 | 2 | 15 | 6 | 6 | 0 | 0 | - | - | 0 | gard . | 4 |
| phenmetrazine, 25 mg. | 1 | 4 | 10 | 7 | 00 | 0 | 2 | 0 | 1 | 1 | 0 | 7 |
| d-amphet. SO, as coated granules, | 0 | 9 | 111 | 20 | 90 | 1 | - | 7 | 0 | 3 | 0 | 1 |
| d- and dl-amphet, as resin | 0 | 00 | 6 | 17 | 14 | 1 | 2 | 0 | - | 0 | 0 | - |
| complexes, 12.5 mg. d- and dl-amphet, as resin | 1 | 111 | 13 | 30 | 17 | 10 | 3 | 0 | 0 | 2 | 0 | 0 |
| complexes, 20 mg. d- and dl-amphet., 20 mg., + Benactyzine, 16 mg., as resin | 0 | 90 | 10 | 27 | = | 13 | 0 | 0 | 7 | 18 | 0 | 0 |
| complexes d- and dl-amphet., 12.5 mg., + Benactyzine, 16 mg., as resin | 0 | 12 | 35 | 48 | 45 | S | 2 | 9 | 0 | 3 | 0 | 0 |
| complexes d- and dl-amphet. as resin complexes, 20 mg., + Tuazole, | 7 | 0 | 1 | 90 | 25 | - | - | - | 0 | 0 | - | 0 |
| 2-phenyl-tertbutylamine resin, | 1 | 1 | 3 | 00 | 14 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| d- and dl-amphet. as resin complexes, 20 mg., + Tuazole, 5 mg. | 0 | 0 | 0 | 0 | 6 | - | 0 | 0 | 0 | 0 | 0 | 0 |

of the side-effects recorded for this agent is lower than that of comparable anorexigenic drugs.

SUMMARY

A precise, controlled study of 10 different anorexigenic agents and a placebo has been conducted and analyzed. The medications were evaluated in 214 patients over a period of eight weeks. Four of the drugs were commercially available amphetamine preparations, four were experimental combinations of amphetamine with two different calmatives, and two were

of the non-amphetamine type.

All medications with the exception of the placebo produced varying degrees of effective appetite control. The weight loss experienced by patients receiving the amphetamine compounds was essentially uniform. The average weight loss per patient per day for all of the amphetamine preparations was 0.22 pound. The stronger 20 mg. d- and dl-amphetamine as resin complexes, with benactyzine resin complex added, produced the greatest weight loss, but this was associated with a greater number of side-effects. The combination of methyl-orthotolyl-quinazolone with d- and l-amphetamine as resin complexes reduced the incidence of side-effects over those obtained with amphetamine alone, with little loss in the anorexigenic activity.

A comparison of weight loss obtained with 2-phenyl-tert.-butylamine as its resin complex, and phenmetrazine, shows a significant difference. The average weight loss per patient per day on phenmetrazine given three times a day was 0.19 pound, as compared to 0.24 pound with 2-phenyl-tert.-butylamine-resinate given once a day. The non-amphetamine drug phenyl-tert.-butylamine as a resin complex produced a more satisfactory weight loss when compared with other medications. The incidence of the side-effects recorded for this agent is lower than that of comparable anorexigenic drugs. From the data presented, it appears that tolerance to this material develops more slowly than to other anorectic agents.

SUMMARIO IN INTERLINGUA

Esseva facite un studio de 10 agentes anorexigene e un placebo con le use de 214 patientes durante periodos de al minus octo septimanas. Quarto del drogas esseva commercialmente disponibile preparatos amphetaminic, quatro esseva combinationes experimental de amphetamina con duo differente calmantes, e esseva de un typo non-amphetaminic. Le perdita medie de peso per die e patiente pro omne le preparatos amphetaminic esseva 0,22 libras. Le combinationes experimental de complexo de d- e dl-amphetamina e resina a excambio de iones e de complexo de methyl-orthotolyl-quinazolona e resina a excambio de iones habeva un reducite incidentia de effectos lateral in comparation con le preparatos que contineva amphatamina sol.

Un comparation del perdita de peso effectuate per le productos non-amphetaminic, complexo de 2-phenyl-tert.-butylamina e resina administrate un vice per die e phenmetrazina administrate tres vices per die, revela un differentia significative. In le caso del prime del duo, le perdita medie de peso per die e patiente esseva 0,24

libras; pro le secunde, 0,19 libras. Le producto non-amphetaminic, complexo de 2-phenyl-tert.-butylamina e resina produceva un plus satisfacente perdita de peso que le altere medicationes. Le incidentia de effectos lateral registrate pro iste agente es plus basse que illo de comparabile drogas anorexigene. Il pare que le tolerantia pro iste droga se disveloppa plus lentemente que le tolerantia pro altere agentes anorectic.

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HYPERCHLORHYDRIA, DUODENITIS AND DUODENAL ULCER: A CLINICAL STUDY OF THEIR INTER-RELATIONSHIPS*

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THE clinical features, roentgen appearance and therapeutic management of peptic ulceration of the duodenum represent familiar concepts in contemporary medical practice. The presence of a constant, barium-filled ulcer niche, with or without secondary roentgenologic signs, constitutes evidence for institution of a reasonably well defined program of extended care. On the other hand, alterations may occur in the mucosal pattern of the duodenum, not infrequently accompanied by hypermotility and/or hypersecretion, in the absence of frank ulceration, a radiologic appearance usually referred to as duodenitis. Other patients, with complaints simulating peptic ulcer, have a completely normal upper gastrointestinal series but demonstrate gastric hyperchlorhydria. These patients who fail to exhibit an active ulcer crater are all too often diagnosed as psychoneurotic, or as having a "nervous stomach" or "functional dyspepsia," and are given inadequate or inappropriate therapy. Yet duodenitis has been considered to be a stage in the development or healing of duodenal ulcer,1,2 and hyperchlorhydria has been implicated as a factor in the pathogenesis of duodenal ulcer. 3, 4, 5 These entities are therefore worthy of further investigation.

Baudin in 1837 first described duodenitis, and noted the association of gastrointestinal bleeding and psychogenic factors. Subsequently, the roent-genologic similarity to duodenal ulcer has been emphasized, the barium-filled crater distinguishing the latter entity. A detailed description of the radiologic appearance of duodenitis was given by Ritvo and Shauffer. This included: spasticity, irritability, and rapid flow of barium (through the duodenum); a coarse mucosal pattern, with thickening of the folds and increase in the depths of the hollows between folds; an irregularly reticular mucosa, usually forming translucent islets lying in a dense network. The radiographic appearance of our duodenitis cases conformed to this description.

Evolution of interest in the problem of duodenitis followed surgical exploration of patients with symptoms simulating those of peptic ulcer. Judd ¹⁰ described 64 gastroduodenal resections which exhibited a grossly

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inflamed duodenal mucosa without evidence of old or recent ulceration. Histologic examination revealed cellular destruction, vascular congestion, edema, and diapedesis of neutrophils and lymphocytes. MacCarty 11 reviewed surgical specimens from 425 cases of duodenal ulcer and 97 cases of duodenitis without ulcer, noting that the symptoms and the radiologic pictures were closely similar between the two groups, and that most of the ulcers were surrounded by inflammatory lesions. Judd and Nagel 12 found duodenitis alone in 10% of 273 cases with clinically suspected duodenal ulcer, and stated that these patients usually had typical ulcer symptoms, often with gross gastrointestinal bleeding. Among 45 surgically proved cases of duodenitis, Kirklin 8 observed typical ulcer distress, with food and alkali relief in 80%, and gross or occult bleeding in 20%. In Rivers' 18 group of 75 patients with surgically verified duodenitis without ulcers, typical ulcer symptoms were present in one third, suggestive ulcer symptoms present in another third, and 12% suffered gross hemorrhage. He concluded that duodenitis is probably the precursor of duodenal ulcer. Puhl 2, 14 and Konjetzny, 15 in exhaustive pathologic studies of resected specimens, introduced the intramucosal erosion (Flachulcus) as the intermediate step between the underlying inflammatory change and the deep, chronic peptic ulcer. These erosions usually healed, leaving mucosal atrophy, but, under special circumstances, progressed to chronic peptic ulcer. The periodicity of symptoms was considered to result from the recurrence and healing of these inflammatory erosions. Several cases were reported in whom resection was not performed initially because only gastroduodenitis was found at surgical exploration. At reoperation, undertaken for recurrent symptoms, true chronic ulcers were present. These authors concluded that duodenitis is the precursor of duodenal ulcer, and that one cannot attribute ulcer symptoms to a gastric neurosis until a pathologically normal antroduodenal segment has been demonstrated.

Bockus ¹⁶ mentioned "peptic duodenitis," but felt that proof of this entity was lacking. He listed multiple factors which he considered to be of etiologic importance in duodenitis: (a) parasitic infestation such as giardiasis, ¹⁷ ancylostomiasis and strongyloidiasis; (b) disease of contiguous organs (liver, pancreas and gall-bladder); (c) stasis of duodenal contents; and (d) diverticula of the duodenum. Doniach and Shiner ¹⁸ failed to demonstrate inflammation in peroral duodenal suction biopsies obtained from 11 patients with "x-ray negative dyspepsia." However, they disregarded as "normal" considerable degrees of lymphocytic infiltration of the mucosa. Furthermore, gastric analyses were not reported, so that their series is not comparable to our patients, who manifested radiologic and/or secretory abnormalities.

Hyperchlorhydria has been repeatedly found as a concomitant of duodenal ulcer, both basally ¹⁹ and after various stimuli. ^{20, 21, 22} Confirmatory results have been the increased gastric pepsin, ^{20, 23} serum pepsinogen ^{28, 24, 25} and urine pepsinogen ^{28, 20, 27} present in such cases. The individual relative

constancy of the basal 28, 29 and histamine-stimulated 22, 29 gastric acid secretion, of urine pepsinogen 27, 30, 81 and of plasma pepsinogen 32, 33 has been amply demonstrated in serial studies of human adults, both with and without ulcers. These secretory parameters thus seem to be characteristic of the individual, although moderate variations occur in relation to emotional stress. 34, 85, 36 Pepsinogen levels, determined on the cord blood of 200 newborns, showed that 12% were hypersecretors from birth. 36 With the above data in mind, it would seem that hyperchlorhydria (i.e., the hypersecretor state) is probably an inborn characteristic which long precedes and predisposes to the development of peptic ulceration. This concept has received ample backing in animal studies. 37, 38 However, duodenal ulcers do occur in the absence of hyperacidity, 15, 22, 39, 40, 41 as was true in approximately one third of our ulcer cases who had gastric analyses performed (table 14). Therefore, the role of hypersecretion per se in the genesis of ulcer symptoms and of the crater itself is unclear.

Since the 1920's the subject of duodenitis has vanished from the literature under the flood of interest in the relationship of gastric hypersecretion to ulcer. Furthermore, only in the last 10 years have clinical hypersecretors been followed to determine their propensity to future ulceration. Weiner et al.⁴² measured serum pensinogen levels in 2.073 unselected Army inductees. Three hundred (15%) were considered hypersecretors, and 63 of these were x-rayed prior to and after from two to four months of basic training. Radiologic evidence of duodenal ulcer was uncovered in nine members (15%) of the hypersecretor group, as contrasted with the absence of such findings among the hyposecretor controls. Mirsky 36 measured serum pepsinogen concentrations in 1,600 children and 4,460 adults. In this still incomplete study, many of the hypersecretors (but none of the hyposecretors) have subsequently developed proved duodenal ulcer. Roth 43 followed a group of patients with hyperchlorhydria after caffeine stimulation, but with negative barium studies and no symptoms. He reported that one third have subsequently developed symptoms and radiologic signs of duodenal ulcer over an unspecified period of time.

Our investigation attempts to delineate the clinical features of radiologically diagnosed duodenitis and duodenal ulcer, and of hyperchlorhydria in subjects with a normal upper gastrointestinal x-ray series. Comparisons will be made among the three groups as to signs and symptoms, complications, and duration and course of the disease. Furthermore, the role of the age at onset of illness, and of apparent provocative factors, will be studied to determine their influence upon the natural history and possible interrelation-

ships of the above clinicoradiologic conditions.

DEFINITIONS

To clarify certain terminology used throughout this paper, the following definitions are given:

1. Ulcer Group: Cases in which, at some time in the course of the illness, an active duodenal ulcer crater and/or a deformed duodenal cap were noted on upper gastrointestinal series. Perforation and pyloric obstruction are considered to be prima facie evidence of a duodenal ulcer. It is also assumed that a scarred and deformed bulb is testimony that an active ulcer was present at some time in the past.2,44 Regardless of the radiologic appearance of the duodenum during the present admission, the patient is included in this Ulcer Group if a crater or deformity was demonstrated at any time.

A. Complicated Ulcers: Subjects who suffered obstruction, perforation or bleeding consequent to the ulcer. Eight of the cases with obstruction or perforation had also hemorrhaged. In this study, gross gastrointestinal bleeding is defined as visible hematemesis and/or melena, confirmed by guaiac determinations or, in two cases, persistent 4-plus positive stool guaiac tests with a hematocrit below 30% (significant occult bleeding). Blood-streaked vomitus following prolonged emesis, a relatively common occurrence after excessive alcoholic intake, is not counted as gastrointestinal

hemorrhage.

B. Simple Ulcers: Ulcer cases without complications.

2. Nonulcer Group: Patients presenting with ulcer-like complaints, but at no time exhibiting an active crater or scarring of the duodenum on barium radiograms. At least one negative stool examination for ova and parasites was obtained in each case, with the exception of two yielding Giardia lamblia. Some patients also had normal cholecystograms and barium enemas, and a few underwent gastroscopy, without significant findings. The only complication observed in these subjects was hemorrhage, since perforation or obstruction automatically placed them in the Ulcer Group (v.s.). This Nonulcer Group was further subdivided into two categories:

A. Duodenitis Group: Cases who, at some time in their illness, demonstrated, on upper alimentary radiograms, duodenal alterations which have been described earlier and are illustrated in figures 1 and 2. Hyperacidity

was a common associated finding.

B. Hyperchlorhydria Group: Cases without radiologic abnormalities, but yielding, on gastric aspiration in the fasting state, after histamine or caffeine stimulation, a maximal free acid greater than 50 and/or total acid greater than 75 clinical units. Doses employed were: histamine phosphate, 0.5 mg. subcutaneously, or caffeine and sodium benzoate, 500 mg: intramuscularly. After withdrawal of the fasting residual and injection of the secretagogue, samples were aspirated every 15 minutes for one hour and titrated with 0.1 N sodium hydroxide to successive end-points with Töpfer's reagent and phenolphthalein indicators. The levels of acidity selected are the upper limits of normal in our hospital, using the technic just outlined. These acid values also conform to the lowest levels found by Polland 21 in

112 patients with duodenal ulcer, using continuous aspiration and the somewhat higher "standard" dose of histamine.

3. Age: Cases were further classified on the basis of age at onset of the illness, as determined from the date of earliest development of complaints consistent with ulcer-type distress. Henceforth, age always refers to the age of the patient at the time of onset of symptomatic disease.

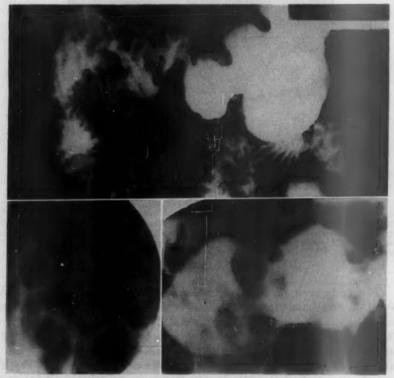


Fig. 1. Severe duodenitis in a 20 year old sailor. At age 16 he had acute, painless, massive hematemesis with a negative gastrointestinal series. For three months prior to the above x-rays he had suffered from "sticking" postprandial epigastric pain, nausea and occasional emesis. Note the marked polypoid change in the mucosa of the bulb, with thickening of mucosal folds extending into the second portion of the duodenum. The lower frames are spot films of the duodenal bulb, with and without compression.

4. Treatment: All patients received a standardized regimen, including a diet progressing from Sippy diet to bland diet, interim milk, antacid gels, phenobarbital and belladonna before meals, initial bed-rest, and discouragement of smoking. Therapy was instituted within 24 hours of admission, and was liberalized at about the same rate in all cases.



Fig. 2. Mild duodenitis in a 37 year old Navy chief. For four months he had been bothered by frequent eructations, controlled with belladonna. Three weeks prior to the above x-rays he developed postprandial epigastric burning distress, relieved by alkali. Note the spastic duodenal bulb, with thickening and irregularity of the mucosal folds extending into the second portion of the duodenum. Spot films, with compression, did not demonstrated. strate a crater.

CASE SELECTION AND DISTRIBUTION

The study reservoir consists of all male, active duty or retired U. S. Naval personnel admitted to the wards of the U. S. Naval Hospital, Newport, Rhode Island, between September, 1955, and April, 1957, inclusive. During this period at least one of the authors was in attendance on the medical service. Two hundred eighty-six consecutive records with gastrointestinal diagnoses were reviewed, including subjects labeled as "Psychogenic Gastrointestinal Reaction." For this study, we selected all 155 cases

TABLE 1 Over-all Distribution by Ages and Diagnoses

| Diagnoses | | Entire Series | | | |
|--|---------------------------------|-------------------------------|--------------------------------|-------------------------------|-----------------------------------|
| w commence floorer | Under 21 | 21-25 | 26-30 | Over 30 | |
| Hyperchlorhydria Duodenitis Duodenal ulcer | 5 (13%) 11 (28%) 23 (59%) | 4 (13%) 3 (9%) 25 (78%) | 9 (24%) 4 (11%) 24 (65%) | 0 (0%) 8 (17%) 39 (83%) | 18 (12%) 26 (17%) 111 (71%) |
| Entire series | 39 (25%) | 32 (21%) | 37 (24%) | 47 (30%) | 155 |

that met the criteria outlined in the above definitions. Of the 111 cases in the Ulcer Group, only nine showed scarring of the bulb without active ulceration. Twenty-six patients exhibited radiologic duodenitis, while the remaining 18 experienced ulcer-like symptoms but showed only hyperchlorhydria. Two additional patients, with these symptoms but no demonstrable abnormalities, were not included in the study.

Distribution of the subjects according to diagnostic category and age is given in table 1. There were no hyperchlorhydria cases above age 30, and a majority (52%) of nonulcer subjects were age 25 or less. By contrast, an

TABLE 2 A Complications Nanulcer Crow

| | - | 1 | * | | | |
|---|----------------------------------|---------------------------------|----------------------------------|--|----------------------------------|--|
| Diagnoses | Bleeding | | Simple | | Totals | |
| Hyperchlorhydria Duodenitis | 8 (44%) 8 (31%) | | 10 (56%) 18 (69%) | | 8 (41%) 6 (59%) | |
| Nonulcer group | 16 (36%) | | 28 (64%) | 4 | 4 | |
| | B. Comp | olications—Ul | cer Group | | | |
| | Under 21 | 21-25 | 26-30 | Over 30 | Entire Group | |
| Obstructed Perforated Bleeding only | 1 1 11 | I 2 4 | 0 5 8 | 4 5 10 | 6 (12%) 13 (25%) 33 (63%) | |
| Complicated Simple | 13 (57%) 10 (43%) | 7 (28%) 18 (72%) | 13 (54%) 11 (46%) | 19 (49%) 20 (51%) | 52 (47%) 59 (53%) | |
| Ulcer group | 23 (21%) | 25 (22%) | 24 (22%) | 39 (35%) | 111 | |
| | C. Comp | lications—En | tire Series | The state of the s | | |
| | Under 21 | 21-25 | 26-30 | Over 30 | Entire Series | |
| Complicated Bleeding only Simple | 18 (46%) 16 (41%) 21 (54%) | 10 (31%) 7 (22%) 22 (69%) | 20 (54%) 15 (41%) 17 (46%) | 20 (43%) 11 (23%) 27 (57%) | 68 (44%) 49 (32%) 87 (56%) | |

ulcer was present in 76% of patients age 21 or older (P < 0.05), and in 83% of those over age 30.

Table 2A demonstrates the essentially similar frequency of bleeding in the hyperchlorhydria and duodenitis groups, and the strikingly high incidence (36%) of gastrointestinal hemorrhage in these subjects without detectable ulcers at any time. Within the ulcer group (table 2B), bleeding accounts for the great majority of complications (85%) in those under age 21, whereas approximately three quarters of the perforated and obstructed cases occurred in patients above 25 years of age. Further, bleeding is significantly more common under the age of 21, with 48% of that age category having gross hemorrhage, as compared with 30% of the entire ulcer group (P < 0.05). Similar statements may be applied to the entire series of subjects, although the differences barely fail to attain statistical validity (table 2C).

CLINICAL COMPARISON OF THE DIAGNOSTIC CLASSES

We now proceed to the comparison of ulcer and nonulcer diseases. The basic problem is the significance of ulcer-like symptoms, either with or without a radiologically visualized duodenal crater or scar. In other words, does the presence or absence of a crater alter the symptoms, signs, course or prognosis of patients with the above type of complaints?

TABLE 3
Chief Complaint

| | High HCl | Duodenitis | Nonulcer | Ulcer | Entire Series |
|-----------------|----------|------------|----------|----------|---------------|
| Pain or burning | 12 (67%) | 13 (50%) | 25 (57%) | 75 (68%) | 100 (65%) |
| Vague distress | 3 (17%) | 7 (27%) | 10 (23%) | 9 (8%) | 19 (12%) |
| G.I. bleeding | 1 (6%) | 3 (12%) | 4 (10%) | 18 (16%) | 22 (14%) |
| Systems review | 2 (11%) | 3 (12%) | 5 (11%) | 9 (8%) | 14 (9%) |

Chief Complaint (Table 3): Pain, or a burning sensation in the abdomen, constituted the chief complaint of the majority (65%) of patients, irrespective of diagnosis. However, the presenting symptom was vague abdominal discomfort in 12%, or upper gastrointestinal bleeding in 14%. Fourteen patients (9%) were admitted for other illnesses, but investigation of ulcer-like symptoms, elicited on review of systems, led to the demonstration of hyperchlorhydria, duodenitis or duodenal ulcer. Pain and bleeding were more common chief complaints among the ulcer category, whereas nonulcer patients more often presented with vague distress (P < 0.02 on an eightfold table).

TABLE 4*
Quality of Discomfort

| | High HCl | Duodenitis | Nonulcer | Ulcer | Entire Series |
|----------|----------|------------|----------|----------|---------------|
| Classic | 8 (45%) | 14 (54%) | 22 (50%) | 60 (56%) | 82 (54%) |
| Vague | 4 (22%) | 6 (23%) | 10 (23%) | 26 (24%) | 36 (24%) |
| Atypical | 6 (33%) | 6 (23%) | 12 (27%) | 21 (20%) | 33 (22%) |

^{*} Only 151 cases are included in tables 4, 5, 6, and 7, since four patients in the ulcer group were "silent" G.I. bleeders who never suffered abdominal discomfort.

Quality of Discomfort (Table 4): Classic ulcer pain, described as hunger, or gnawing or burning in character, 45 occurred in only 54% of the patients. A fair proportion of individuals were unable to define the quality of their discomfort, indicating only a vague, unpleasant sensation localized in the upper abdomen. Specific but atypical forms of distress, described as "stick-

ing," "sharp," "knifelike," "knotlike," "cramping," "pressure" or "tightness," were experienced by the remaining 22%. There were no significant differences in the frequency of the various types of distress among the three groups. Noteworthy is the nearly identical incidence of classic pain in the ulcer and nonulcer groups.

TABLE 5 Location of the Discomfort

| | High HC1 | Duodenitis | Nonulcer | Ulcer | Entire Series |
|-----------------|----------|------------|----------|----------|---------------|
| Midepigastrium | 14 (78%) | 21 (81%) | 35 (80%) | 92 (86%) | 127 (84%) |
| Other abdominal | 3 (17%) | 5 (19%) | 8 (18%) | 10 (9%) | 18 (12%) |
| Substernal | 1 (5%) | 0 (0%) | 1 (2%) | 5 (5%) | 6 (4%) |

Location of the Discomfort (Table 5): Primary location of the pain in the midepigastrium was noted by 84% of all patients, and was the only purportedly "classical" 45 clinical feature of duodenal ulcer which obtained in over 80% of the subjects in this series. Another 12% suffered their main discomfort in other areas of the abdomen, as follows: periumbilical, eight; right upper quadrant, four; left upper quadrant, four; diffuse, two. In 4% (six cases), the distress was substernal. None was afflicted with pain principally in the back or lower abdomen. There are no significant differences among the various diagnostic categories.

Radiation of the pain occurred in 24% of the patients, including 25% of the ulcer and 20% of the nonulcer groups. Pain radiated to the following sites: back, 12; substernal area, nine; umbilicus and lower abdomen, nine; upper quadrants, six. The numbers are too small to warrant comparison between groups.

TABLE 6 Timing of the Pain

| | High HCl | Duodenitis | Nonulcer | Ulcer | Entire Series |
|---|---|--|---|--|---|
| ≥ 1 hour p.c. < 1 hour p.c. Before meals No relation Night pain | 11 (69%) 1 (6%) 2 (13%) 3 (19%) 6 (38%) | 11 (52%) 2 (10%) 9 (43%) 2 (10%) 4 (19%) | 22 (60%) 3 (8%) 11 (30%) 5 (14%) 10 (27%) | 50 (60%) 4 (5%) 17 (21%) 6 (7%) 33 (39%) | 72 (60%) 7 (6%) 28 (23%) 11 (9%) 43 (36%) |
| Cases stated | 16. (89%) | 21 (81%) | 37 (84%) | 84 (79%) | 121 (80% |
| Total cases | 18 | 26 | 44 | 107 | 151 |

Timing of the Pain (Table 6): Distress occurred at least one hour after meals in the majority (60%) of subjects. Nocturnal pain, awakening the patient sometime after midnight, was described by 36% of the entire series, while 23% noted distress immediately before meals, i.e., "when the stomach was empty." It is striking that 9% could not relate their distress to meals, and 6% were bothered less than one hour postprandially. Since many subjects suffered various combinations of the above pain syndromes, the figures total more than 100%. In one fifth of the records, no statement was made regarding timing of the pain.

As defined by textbook description,^{41, 46} ulcer pain occurs one hour or more postprandially, and frequently at night. In our series, however, such timing could not be selectively related to the presence of an ulcer crater, as none of the apparent differences among the groups achieves statistical significance.

TABLE 7
Agents Relieving Pain

| | High HCl | Duodenitis | Nonulcer. | Ulcer | Entire Series |
|----------|----------|------------|-----------|----------|---------------|
| Food | 8 (44%) | 11 (42%) | 11 (43%) | 36 (34%) | 55 (36%) |
| Milk | 7 (39%) | 6 (23%) | 13 (30%) | 45 (42%) | 58 (38%) |
| Antacids | 10 (55%) | 12 (46%) | 22 (50%) | 54 (50%) | 76 (50%) |

Relief of Pain by Various Agents (Table 7): Amelioration of the ulcer discomfort was obtained with food in 36%, milk in 38%, and antacids in 50% of the patients. A few others considered hot liquids or even beer to be beneficial. It is realized that the figures may be biased by the fact that some patients may not even have tried a given agent, much less obtained benefit from its use. Nonetheless, each agent granted relief to similar proportions of the ulcer and nonulcer groups.

TABLE 8
Associated Symptoms

| | High HCl | Duodenitis | Nonulcer | Ulcer | Entire Series |
|---------------------|----------|------------|----------|----------|---------------|
| Heartburn | 3 (17%) | 7 (27%) | 10 (23%) | 20 (18%) | 30 (19%) |
| Anorexia | 5 (28%) | 4 (15%) | 9 (21%) | 16 (14%) | 25 (16%) |
| Nausea | 8 (44%) | 13 (50%) | 21 (48%) | 38 (34%) | 59 (38%) |
| Vomiting | 8 (44%) | 18 (69%) | 26 (59%) | 42 (38%) | 68 (44%) |
| Belching and flatus | 7 (39%) | 11 (42%) | 18 (41%) | 31 (28%) | 49 (32%) |
| Diarrhea | 5 (28%) | 5 (19%) | 10 (23%) | 5 (5%) | 15 (10%) |
| Weight loss | 6 (33%) | 3 (12%) | 9 (21%) | 24 (22%) | 33 (21%) |

Associated Symptoms (Table 8): Other gastrointestinal symptoms often accompany the characteristic localized discomfort of peptic ulcer. 45 In our study, these occurred with the following frequency: heartburn, 19%; anorexia, 16%; nausea, 38%; vomiting, 44%; excessive flatus and belching, 32%; waterbrash and regurgitation (without emesis), 5%; diarrhea, 10%; weight loss of more than 10 pounds during any single exacerbation, 21%. The frequency of constipation was not studied, since our records did not document the role of the antacid gels in producing this symptom. The low frequency of water brash reflects the failure of inquiry in this regard, and will not be further analyzed.

With the exception of weight loss, all of the above symptoms were more frequently present in the patients without ulcers. This is significant for vomiting (P < 0.02), and highly significant for diarrhea (P < 0.001). The differences for nausea, excess flatus and belching are impressive but barely fail to achieve statistical significance.

TABLE 9 Gross Gastrointestinal Bleeding

| TO SHE WAS A SHEET | High HCl | Duodenitis | Nonulcer | Ulcer | Entire Series |
|--|-------------------------------|-------------------------------|-------------------------------|----------------------------------|----------------------------------|
| Hematemesis only Melena only Both together | 5 (72%) 1 (14%) 1 (14%) | 4 (57%) 2 (29%) 1 (14%) | 9 (64%) 3 (21%) 2 (14%) | 11 (27%) 18 (44%) 12 (29%) | 20 (36%) 21 (38%) 14 (25%) |
| Total bleeding | 7 (39%) | 7 (27%) | 14 (32%) | 41 (37%) | 55 (36%) |
| Total cases | 18 | 26 | 44 | 111 | 155 |

Gross Gastrointestinal Bleeding (Table 9): Hematemesis and/or melena occurred in 36% of all the subjects. Of these bleeders, 36% suffered hematemesis without melena, 38% had melena without hematemesis, and 25% experienced both forms of hemorrhage. As previously noted (table 2), the incidence of gross hemorrhage was essentially as high in the nonulcer group (32%) as in the ulcer group (37%).* However, as a sixfold analysis reveals, there are significant differences between the ulcer and nonulcer patients regarding the type of bleeding manifested (P < 0.05). Hematemesis alone is two and one-half times as frequent in the nonulcer group, while melena (with or without hematemesis) is twice as common among bleeders in the ulcer group (73% vs. 35%, P < 0.02). We wish to reemphasize that blood-streaked emesis is not counted as hemorrhage, and that the incidence of moderate and heavy alcoholism was identical (55%) among the bleeders in the ulcer and nonulcer categories.

TABLE 10 **Abdominal Tenderness**

| | High HCl | Duodenitis | Nonulcer | Ulcer | Entire Series |
|-----------------|----------|------------|----------|----------|---------------|
| Epigastric | 5 (28%) | 6 (23%) | 11 (25%) | 34 (31%) | 45 (29%) |
| Other abdominal | 7 (39%) | 5 (19%) | 12 (27%) | 18 (16%) | 20 (19%) |
| No tenderness | 6 (33%) | 15 (58%) | 21 (48%) | 59 (53%) | 80 (52%) |

Abdominal Tenderness (Table 10): Approximately one-half (52%) of the entire series of patients did not have abdominal tenderness on physical examination, including 53% of patients with ulcers. Hyperchlorhydria cases showed the highest incidence (67%) of this physical sign, despite

^{*}Differences from table 2 are due to omission from table 9 of the two cases with significant occult bleeding and the concurrence of hemorrhage in three of the obstructed and five of the perforated ulcers in table 2.

persistently negative roentgen studies of the upper alimentary tract. This frequency was considerably—but not significantly—higher than the prevalence of tenderness in the duodenitis and ulcer groups (42% and 47%, respectively).

All diagnostic categories demonstrate an approximately equal incidence of *epigastric* tenderness. Consequently, the higher frequency of abdominal tenderness in the hyperchlorhydria patients derives from the preponderance of nonepigastric tenderness (39%) found in these cases. Among the 30 patients with tenderness outside the epigastrium, the locations were: right upper quadrant, 15; periumbilical or below, eight; diffuse in the abdomen, five; left upper quadrant, two (both had associated gastritis). The distribution of nonepigastric tenderness was similar in the ulcer and the non-ulcer groups.

TABLE 11
Family History and Emotional Factors

| | High HCl | Duodenitis | Nonulcer | Ulcer | Entire Series |
|-------------------|----------|------------|----------|----------|---------------|
| Familial ulcer | 2 (11%) | 4 (15%) | 6 (14%) | 12 (11%) | 18 (12%) |
| Emotional factors | 11 (61%) | 13 (50%) | 24 (55%) | 58 (52%) | 82 (53%) |

Family History and Emotional Factors (Table 11): A positive family history was considered to be present whenever some member of the *immediate* family (parents or siblings) had experienced a peptic ulcer. Neither other gastrointestinal diseases ("nervous stomach," ulcerative colitis, gastric cancer, etc.) nor other psychosomatic or nervous disorders were accepted, although these were present in many of the genealogies. According to these criteria, a family history of ulcer was elicited in only 12% of the 155 cases, and occurred with the same frequency in each diagnostic class. However, a significantly higher incidence of familial ulcer (20%) occurred in patients whose symptoms began prior to age 25, rather than later (5%) (P < 0.01).

Emotional factors were considered to be important whenever: (1) a specific relationship was noted between flareups of ulcer symptoms and periods of emotional tension; in this series, the most common precipitating factors were difficulty with wives or superiors, or promotion to a post demanding increased responsibility; (2) physical examination revealed evidence of marked anxiety, such as cold, moist palms, onychophagy, emotional lability, or exceptional dependency upon or hostility toward the attending physician. It is agreed that such categorization is largely subjective, but it was performed in the absence of prior knowledge of this investigation, and is therefore unbiased. Emotional factors, as defined, were evident in 53% of the subjects, with similar prevalence among the various diagnostic categories. Approximately half of these subjects were evaluated by a psychiatrist, and were almost always classified as immature, passive-aggressive or passive-dependent personalities, in agreement with Alexander.

TABLE 12
Usage of Provocative Agents

| | | Nonulcer | Ulcer | Entire Series |
|----------|-----------------------------------|--|--|--|
| Alcohol | None Mild Moderate Heavy | 5 (13%) 14 (35%) 9 (23%) 12 (30%) | 23 (23%) 26 (26%) 31 (31%) 20 (20%) | 28 (20%) 40 (29%) 40 (29%) 32 (23%) |
| | Stated | 40 | 100 | 140 |
| Tobacco | None Mild Moderate Heavy | 7 (18%) 13 (33%) 11 (28%) 8 (21%) | 13 (13%) 18 (18%) 46 (46%) 24 (24%) | 20 (14%) 31 (22%) 47 (41%) 32 (23%) |
| | Stated | 39 | 101 | 140 |
| Coffee | None Mild Moderate Heavy | 0 (0%) 7 (35%) 10 (50%) 3 (15%) | 14 (25%) 15 (27%) 15 (27%) 11 (20%) | 14 (19%) 22 (29%) 25 (33%) 14 (19%) |
| | Stated | 20 | 55 | 75 |
| Total Ca | ises | 44 | 111 | 155 |

Use of Provocative Agents (Table 12): Alcohol, 48 tobacco 49 and coffee 50 have been implicated as agents aggravating duodenal ulcer. For purposes of analysis, we have arbitrarily delineated three degrees of consumption of each agent:

| Use | Alcohol | Cigarettes | Coffee (cups/day) |
|----------|---|------------|-------------------|
| Mild | Occasionally several drinks, never becoming intoxicated. | 0-10/day | 0-5 |
| Moderate | Intermittent heavy binges or almost daily social drinking. | 11-20/day | 6-10 |
| Heavy | Steady and excessive drinking, with frequent intoxication, | 21 or more | 11 or more |

When the entire series is considered, degrees of usage were similar for each of the three agents: 14 to 20% abstained, 22 to 29% were mild consumers, 29 to 41% were moderate consumers, and 19 to 23% were heavy consumers. There was a definite tendency for heavy imbibers of one agent to have a similarly excessive intake of the others as well. It should be noted that these figures refer to spontaneous usage, prior to the diagnosis of gastrointestinal disease, and therefore antedating the imposition of medical restrictions.

Differences in alcohol consumption between the ulcer and nonulcer groups were not significant. Many more moderate and heavy smokers were found in the ulcer group (69%) than in the nonulcer group (49%) (P < 0.05). Coffee drinking was more common among nonulcer subjects (100%) than among those with radiologically demonstrable craters (75%).

Though this difference is significant (P < 0.05), the lack, in over half the records, of a statement regarding coffee usage renders this comparison of dubious validity.

TABLE 13
Intolerance to Provocative Agents

Only percentages of subjects using the various agents are noted. Actual numbers of cases are not given, to avoid making the table too cumbersome.

| | High HCl | Duodenitis | Nonulcer | Ulcer | Entire Series |
|---------|----------|------------|----------|-------|---------------|
| Alcohol | (46%) | (32%) | (37%) | (35%) | (36%) |
| Tobacco | (18%) | (10%) | (13%) | (19%) | (18%) |
| Coffee | (45%) | (33%) | (40%) | (32%) | (34%) |
| Fats | (17%) | (27%) | (23%) | (32%) | (30%) |
| Spices | (39%) | (8%) | (20%) | (34%) | (30%) |

Intolerance to Provocative Agents (Table 13): We have determined, for each agent, the proportion of patients actually using that agent who professed increased symptomatology, or the induction of bleeding, consequent to its use. More than 80% of the smokers noted no aggravation of distress from the use of tobacco, while each of the other agents was found to produce intolerance in about one third of the patients employing that agent. There were no significant differences between the ulcer and the nonulcer groups, but, with the exception of fatty foods, patients with hyperchlorhydria were more often intolerant to a given agent than were duodenitis patients. This is significant only for spices, intolerance to which is five times as common among subjects with hyperchlorhydria (P < 0.02).

TABLE 14
Gastric Analyses (Stimulated)

| Acidities | High HCl | Duodenitis | Nonulcer | Ulcer | Entire Series |
|---|-------------------------------------|----------------------------------|-------------------------------------|------------------------------------|-------------------------------------|
| Cases {Free > 50° with {Total > 75° Average {Free Maximal {Total | 16 (89%) 16 (89%) 95° 127° | 7 (70%) 7 (70%) 85° 95° | 23 (82%) 23 (82%) 92° 115° | 27 (63%) 23 (54%) 75° 91° | 50 (70%) 46 (64%) 82° 101° |
| Gastrics done | 18 | 10 | 28 | 43 | 71 |
| Total cases | 18 | 26 | 44 | 111 | 155 |

Gastric Analyses (Table 14): Gastric aspirations were performed as previously described (see Definitions), with all medications discontinued during the preceding 48 hours. Since it was common to find no free acid in the fasting, overnight, residual gastric juice, but a markedly elevated acidity in the stimulated specimens, we studied only maximal concentrations after histamine or caffeine injection.

In all diagnostic categories, the average maximal free acidity and total

acidity were well above the normal range, and the great majority of cases were hypersecretors. Unfortunately, gastric analysis was performed in only a minority of the ulcer and duodenitis subjects, but our finding that 37% of the ulcer patients were normosecretors is in agreement with the data of others. 15, 22, 41 The lower percentage of hypersecretors in the duodenitis and ulcer groups (P < 0.02) results from the fact that only in the hyperchlorhydria group was hypersecretion a requirement for inclusion in this study. The presence of the hyperchlorhydria subjects in the nonulcer group also accounts for the higher incidence of hypersecretors in this category (82%), as compared with ulcer patients (63%) (P < 0.05), since the unbiased duodenitis and ulcer groups are statistically indistinguishable.

TABLE 15 **Duration of Symptoms**

| | High HCl | Duodenitis | Nonulcer | Ulcer | Entire Series |
|--|--|---|---|--|--|
| 0-6 months 7-24 months 3-9 years 10 years or more | 10 (56%) 4 (22%) 3 (17%) 1 (6%) | 12 (46%) 8 (31%) 3 (12%) 3 (13%) | 22 (50%) 12 (27%) 6 (14%) 4 (9%) | 31 (28%) 31 (28%) 34 (31%) 15 (14%) | 53 (34%) 43 (28%) 40 (26%) 19 (12%) |
| Average duration (years) | 1.52 | 2.58 | 2.15 | 3.87 | 3.38 |

Duration of Symptoms (Table 15): The duration of illness was estimated from the alleged date of onset of ulcer-like complaints. These approximations represent a discontinuous variable, and are therefore not amenable to tests of the significance of differences between means. However, after grouping, it is evident that duodenal ulcer was associated with a longer illness than was duodenitis, which in turn was associated with a longer history than was hyperchlorhydria. The differences between the ulcer and nonulcer grows are significant (P < 0.05), but those between the hyperchlorhydria and duodenitis categories are not. The presence, in the duodenitis group, of patients with illness lasting 10 or more years serves to raise the average duration of symptoms beyond that of the hyperchlorhydria group. Other significant differences are the higher incidence of duration of less than two years (P < 0.02), and duration of zero to six months (P < 0.01) in the nonulcer patients.

TABLE 16 Course of the Illness

| | | High HC1 | Duodenitis | Nonulcer | Ulcer | Entire Series |
|---|-------------|----------|------------|----------|----------|---------------|
| 1 | Acute | 9 (50%) | 10 (39%) | 19 (43%) | 25 (23%) | 44 (28%) |
| | Chronic | 8 (44%) | 6 (23%) | 14 (32%) | 36 (32%) | 50 (32%) |
| | Progressive | 1 (6%) | 8 (31%) | 9 (20%) | 33 (30%) | 42 (27%) |
| | Regressive | 0 (0%) | 2 (8%) | 2 (5%) | 17 (15%) | 19 (12%) |

Course of the Illness (Table 16): To analyze the essentially continuous spectrum of the natural history of the disease, we arbitrarily define four different clinical courses:

Acute: History of a single, uninterrupted, symptomatic episode of six months' duration or less.

Chronic: History of a single, uninterrupted episode of more than six months' duration, or recurrent episodes with identical x-ray findings on each occasion.

Progressive: Recurrent symptomatic exacerbations, with radiologic findings changing from less advanced to more advanced stages of the ulcer diathesis on successive recrudescences.

Regressive: Recurrent episodes, with findings changing toward the less advanced stages during successive symptomatic exacerbations.

At this point, we define the term *ulcer diathesis* as a state of chronic, relapsing upper abdominal symptoms, usually of the "ulcer type," associated with abnormalities in the gastroduodenal portion of the alimentary tract to account for the complaints. Four stages of this diathesis are recognized:

- 1. Symptoms with hyperchlorhydria, but a normal gastrointestinal x-ray series.
- 2. Duodenitis without ulceration by barium radiography.
- 3. Duodenal ulcer crater or scar demonstrated radiologically.
- 4. Development of complications consequent to any stage 1 through 3.

Any subject whose course moves from (1) toward (4) falls in the progressive class, the reverse being regressive. Of course, one or more of the intervening phases may not have been documented in the individual case.

Of the 111 cases having a prolonged course, 61 (55%) demonstrated different stages of the diathesis during successive exacerbations, with the progressive course twice as common as the regressive course. Within this same group, five times as many patients maintained (chronic) or advanced (progressive) the stage of their illness with time, as opposed to those (regressive) who lessened the severity of their diathesis as it recurred. This difference is significant (P < 0.02).

Forty-five per cent of the ulcer cases demonstrated a change in the phase of their illness on successive examinations, with two thirds of these having a progressive course. Therefore, 30% of the ulcer subjects had previously undergone barium studies which failed to demonstrate a crater or scar.

An acute course was significantly more common in patients without an ulcer (43%) than in those with craters (23%) (P < 0.02). However, this is a biased figure, since the hyperchlorhydria group cannot regress, and complications other than bleeding are excluded in nonulcer patients.

Prior Hospitalization and Barium Examinations (Table 17): Nearly 40% of all patients had previously been hospitalized because of ulcer-like

TABLE 17 Prior Hospitalization and Radiography

| | High HCl | Duodenitis | Nonulcer | Ulcer | Entire Series |
|---|----------|------------|----------|----------|---------------|
| Patients with prior admissions Total admissions Cases with prior x-rays | 5 (28%) | 5 (19%) | 10 (23%) | 50 (45%) | 60 (39%) |
| | 6 | 7 | 13 | 104 | 117 |
| | 3 (17%) | 6 (23%) | 9 (20%) | 65 (59%) | 74 (48%) |

symptoms, and almost half the entire series had had one or more barium studies of the upper alimentary tract exclusive of the present admission. As can be seen from the total number of prior hospitalizations accumulated, multiple previous admissions were common, especially in the ulcer group. Prior admissions and prior x-ray studies occurred with much greater frequency among the ulcer group than among the nonulcer group (P < 0.01 and P < 0.001, respectively).

TABLE 18 Symptomatic Relief on Therapy

| Treatment Days | High HCl | Duodenitis | Nonulcer | Ulcer | Entire Series |
|------------------------|-------------------------------|--------------------------------|-------------------------------|----------------------------------|----------------------------------|
| 0-7 8-14 over 14 | 14 (88%) 2 (12%) 0 (0%) | 16 (70%) 4 (17%) 3 (13%) | 30 (77%) 6 (15%) 3 (8%) | 64 (68%) 16 (20%) 10 (12%) | 84 (71%) 22 (18%) 13 (11%) |
| Cases stated | 16 | 23 | 39 | 80 | 119 |
| Total cases | 18 | 26 | 44 | 111 | 155 |

Symptomatic Relief on Therapy (Table 18): Symptomatic response to our standard regimen was measured by the number of days required for complete cessation of ulcer-like pain and/or manifestations of gastrointestinal bleeding. Not included in this tabulation are 16 patients who underwent surgery for ulcer complications, and 20 other cases whose records lacked a precise statement concerning the duration of complaints after admission. The outstanding feature of these data is the rapidity of disappearance of ulcer-like symptoms in a hospital setting. None of the hyperchlorhydria subjects was symptomatic after two weeks, and two thirds of those with craters were asymptomatic within one week. There were no essential differences in the response rates of the three groups.

TABLE 19 Radiologic Ulcer Healing

| Not repeated Heal in < month Heal 1-2 months Not healed | 11 55 (75%) 16 (22%) 2 (3%) | Repeat Exam Findings Entirely normal Residual duodenitis Residual deformity | 24 (34%) 16 (23%) 33 (47%) |
|--|--------------------------------------|--|----------------------------------|
| Repeat exams | 73 | Total healed ulcers | 71 |
| Total cases | 84 | (present admission only) | |

Radiologic Ulcer Healing (Table 19): In the large majority of cases, a repeat gastrointestinal series was performed four weeks following admission. These follow-up studies were essentially limited to those patients who demonstrated a duodenal ulcer on the initial radiograph taken during the present hospitalization within four days after admission. There were 84 such cases, of whom 11 did not have follow-up x-rays. Of those repeated, 78% healed within one month, and 97% within two months. Healing resulted in three types of roentgenologic appearance of the bulb on reëxamination: (a) a completely normal looking duodenum (34%); (b) residual duodenitis without a crater (23%); (c) residual deformity due to scarring of the bulb (47%). In two cases, both duodenitis and deformity were seen.

Forty-one patients had duodenitis without an ulcer on the initial barium study of the present admission. Only 12 had repeat studies, usually due to persistent symptoms. Seven of these 12 failed to heal the duodenitis after a month of therapy, representing 17% of the 41 cases. This is a minimal figure, but it is similar to the 22% of ulcer cases who were likewise refractory to one month of treatment.

DISCUSSION

Our series of patients presented a unique opportunity to study the natural history of the ulcer diathesis, particularly cases with no demonstrable crater. This fortunate circumstance evolved from the military policy requiring admission of any individual ill enough to be unable to perform his full duties. Consequently, service personnel are hospitalized and x-rayed very soon after the development of persistent or recurrent gastrointestinal complaints, resulting in frequent studies serially documenting the radiologic appearance of the duodenum during each attack.

The striking similarity of clinical features among the ulcer, duodenitis and hyperchlorhydria groups is clearly demonstrated in our study. Symptoms and signs classically associated with ulcer were present with high frequency, irrespective of the presence or absence of a duodenal niche or scar on barium examination. Admittedly, the incidence of "classic" symptoms tended to be higher in the ulcer group (tables 3–10), but these differences were significant in only three areas:

- A. Chief Complaint (Table 3): Pain and bleeding were more common among ulcer cases, whereas nonulcer subjects more often presented with vague abdominal distress.
- B. Associated Symptoms (Table 8): Vomiting and diarrhea were much more frequent in patients without ulcers.
- C. Bleeding (Table 9): Melena was much more prevalent in the ulcer group, hematemesis in the nonulcer group, though gross hemorrhage was equally common in both.

Differences noted under (A) and (B) are those of degree rather than kind, the greater frequency of vague (A) and functional (B) symptoms in

those without craters possibly reflecting heightened autonomic reactivity. Differences in the quality of bleeding may be similarly explained. Thus increased gastric irritability and motility in nonulcer patients may favor regurgitation of the irritating hemorrhagic contents, resulting in hematemesis, while the less abnormal motility in ulcer subjects favors normal

prograde channeling of the blood, with consequent melena.

In addition to this similarity of symptom complexes, the same agents aggravate the discomfort of both ulcer and nonulcer groups (table 13), and identical therapeutic measures grant symptomatic relief to both groups (table 7) with approximately equal rapidity (table 18). These facts indicate that the mechanisms producing the distress are probably similar in the three diagnostic categories, and that the symptoms certainly cannot be attributed to ulceration itself. Corroboratory evidence is the presence of painless bleeding in four ulcer patients but in none of the nonulcer patients, and the rapid disappearance of pain under therapy (table 18), well before healing of the crater could be expected to have occurred. 51 Other possible causes of "ulcer" discomfort are hyperacidity, duodenal inflammation, and hypermotility, any of which could quickly disappear on standard ulcer management. However, the absence of hyperchlorhydria in many of our patients (table 14), and the clearing of symptoms despite residual duodenitis on follow-up x-rays (table 19), tend to exclude these two phenomena as the source of the discomfort in these patients. We have no evidence regarding hypermotility.

Demonstration of closely similar symptoms and response to the same therapy do not, by themselves, establish the identity of the three diagnostic categories. However, this circumstantial evidence is strongly supported by the free transition among the three stages of the diathesis exhibited by many of our patients. Interchange between at least two of the three radiologic appearances was noted, during symptomatic periods, in 55% of our cases with a history of multiple episodes (table 16). Under therapeutic attack, furthermore, 22% of patients who healed an ulcer (table 19) showed residual duodenitis, while another 34% showed radiologically normal duodenal loops. frequently with accompanying hyperchlorhydria. It is evident that various combinations of hyperchlorhydria, duodenitis and peptic ulcer may be found at different times in a single patient, either during relapses manifesting identical symptoms, or during periods under therapy. These clinical states therefore represent interrelated stages of the same pathophysiologic entity,

the duodenal ulcer diathesis.

Table 15 shows that, the longer a patient has had symptoms, the more likely it is that an ulcer crater or scar will be found, or that radiologic duodenitis will be observed, rather than simple hyperchlorhydria. The significantly greater frequency of earlier barium studies and previous hospitalizations among ulcer patients (table 17) also attests to the longer duration of symptoms in this group. This does not imply that all ulcer cases are of long standing, or that all patients with duodenitis or hyperchlorhydria have been ill for a short period of time, but the trend is definitely in this direction.

Although interchange among the stages on successive episodes may occur in any direction, the course of the illness is twice as commonly progressive toward ulcer as the reverse (table 16). Under appropriate therapy, however, ulcers often leave residual duodenitis or hyperchlorhydria as they disappear (table 19). Hyperchlorhydria may also remain after healing of duodenitis. By contrast, in no instance did a subject, during the period of careful in-patient therapy, progress from hyperchlorhydria to duodenitis, or from duodenitis to ulcer. One patient did advance from duodenitis to ulcer during a one-month period of persistent symptoms, but he had received inadequate out-patient treatment over that interval.

All the above facts strongly indicate that the usual sequence in the development of the peptic ulcer diathesis is hyperchlorhydria to duodenitis to ulcer, justifying our use of the term "progressive" to describe such a course.

Table 1 attests to the greater likelihood of finding an ulcer in patients with onset of symptoms later in life. This may result from a lower pain threshold in young people, causing significant distress earlier in each attack, with x-rays therefore performed before the crater has had an opportunity to develop. An alternative explanation is that the resistance of the duodenal mucosa is diminished in older people, who are therefore more prone to progress to frank ulceration when the setting develops which induces a relapse. The latter is unlikely to apply in our series, where age comparisons were made about the dividing point of 25 years, and all but four persons were under age 40. Whatever the cause, people with a later onset and those with a longer duration of symptoms (tables 1 and 15) exhibit a higher incidence of ulcer. It follows that, the older a person at the time he is studied, the more likely it is that he will fall into the ulcer category.

Provocative agents (table 12), which have been implicated as aggravating the ulcer diathesis, could conceivably promote transition from one stage to another. In our data, moderate and heavy smoking was the only habit significantly more prevalent in the ulcer category. However, cause and effect cannot be easily differentiated here.

Hyperacidity was prominent in all three diagnostic classes, and average free and total acidity (table 14) were approximately the same for the ulcer and the duodenitis subjects. Evident emotional factors and a positive family history of ulcer were equally prevalent among the three diagnostic categories (table 11). Therefore, these factors do not predispose to formation of an ulcer crater per se, although they may provoke development or aggravation of symptoms.

Our figures do not demonstrate a significantly higher incidence of nightpain, weight loss, abdominal tenderness or localized epigastric tenderness in patients with an actual ulcer niche. These symptoms and signs thus cannot be designated as indicators of ulceration, and the results in table 10 also contradict any argument which attributes abdominal tenderness to the duodenitis surrounding the ulcer crater. Diarrhea (table 8) was strikingly more manifest in the nonulcer group, but five ulcer patients also had diarrhea. Gross hemorrhage, without pain, was present only in the ulcer category. However, the relatively small number of cases involved would preclude general application of these criteria without further studies. Clearly, it is impossible, without radiologic study and in the absence of telltale complications, to ascertain clinically the stage at which the ulcer diathesis has come

to rest in a given patient during a given attack.

Even the radiologic criteria are subject to error, since clear demonstration of the ulcer niche may be hindered by any one of a number of factors, such as shallowness of the crater, or the obscuring of the crater by scarring, by the mucosal irregularities of duodenitis, or by clots present during an acute hemorrhage. 52 Available estimates are that about 10% of all gastrointestinal lesions are not visualized radiologically, 58 and that approximately 5% of duodenal ulcers evade detection during an adequate upper gastrointestinal series. It is therefore inevitable that, in our study, a similar small percentage of ulcer cases was falsely classified in the nonulcer group. This may be especially applicable to the hyperchlorhydria group, where it would seem likely that the seven cases with gross hemorrhage had small mucosal ulcerations or erosions despite negative barium examination, in agreement with the pathologic studies of Puhl 2 and Kirklin.8 However, Pape and Hackensellner 54 reported 12% of their bleeders had an entirely normal gastroduodenal mucosa, while another 27% showed inflammatory lesions without ulceration.

The greater likelihood of demonstrating an ulcer after multiple x-rays also offers an alternate explanation for the data in tables 15, 16 and 17. These were interpreted as demonstrating progression of the diathesis from hyperchlorhydria to duodenitis to ulcer, and the longer duration of illness before an ulcer develops. Conversely, it might be surmised that an ulcer was present all along, and that cases of longer duration were more frequently examined radiologically, and consequently presented a better opportunity to discover the crater. Another possible weakness in our study is the lack of gastroscopic examination, since gastritis often causes symptoms indistinguishable from those of duodenal ulcer. 55 On the other hand, the two diseases are often associated.14,56 These points raise theoretic objections to our thesis, but do not negate the practical implications thereof. Furthermore, our conclusions, based on radiologic diagnoses alone, are essentially identical with those of studies, cited in the Introduction, which utilized pathologic material only. 18, 14 Consequently, we believe that, with the small error noted, the radiologic pictures correspond to the pathologic entities.

In our opinion, the foregoing data are best explained by the theory that hyperchlorhydria, duodenitis and duodenal ulcer all constitute stages of the peptic ulcer diathesis. The hypersecretor then represents the reservoir from which the diathesis develops. Under periods of emotional stress and/or increased use of the provocative agents, symptoms appear and inflammation

of the duodenum may occur and progress to true ulceration. With each relapse, some patients traverse the sequence so rapidly that an ulcer is invariably present by the time symptoms become severe enough to warrant radiologic examination. Others, with a less potent inflammatory process and/or lower threshold for symptoms, may be caught in the preinflammatory or preulcerative stages. Under therapy, the majority of subjects completely heal their craters and inflammation, and then undergo the same progression through duodenitis to ulcer with each exacerbation unless the relapse is interrupted by appropriate medical management. Duodenitis is thus conceived as a way-station on the path to developing, or to the process of healing, a duodenal ulcer, a formulation advanced by Puhl over 30 years ago,14

although he denied the role of hyperacidity in ulcerogenesis.

While the above postulation awaits more conclusive proof than is afforded by our study, the practical implications cannot be disregarded. The population examined has repeatedly demonstrated the evolution of a normal upper gastrointestinal series to one exhibiting, on subsequent study, active ulceration, inflammation, or deformity of the bulb. It has also illustrated the inability to distinguish clinically among the stages of the ulcer diathesis, and the propensity of all these patients to suffer gross gastrointestinal bleeding. It follows that patients with ulcer-like symptoms, but without a roentgenoscopically proved crater, cannot be dismissed as functional or psychosomatic problems, especially if they are hypersecretors or show radiologic duodenitis. Certainly, all such symptomatic patients with normal x-rays should have a gastric analysis performed; 43 once the diathesis is established by secretory and/or radiologic investigations, there is no need for repeated x-ray examinations except to elucidate the nature and extent of complications (e.g., obstruction). This would save countless hours and dollars, and greatly limit radiation exposure of these usually young individuals during their reproductive period.

The efficacy and desirability of a protracted and rigid ulcer regimen in this group, as suggested by Puhl,2 remain to be established, for it is unknown whether continued maintenance of "physiologic stomach rest" will avert future ulceration. Duodenitis itself may be longstanding, symptomatic, and the cause of significant hemorrhage (tables 9 and 15), and be as resistant to healing as a duodenal ulcer (table 19). Subjects with duodenitis therefore should probably receive careful treatment of a type appropriate for patients with proved ulcers, especially since some may actually have an ulcer undetected by barium study. We feel similarly about hyperchlorhydria, although our evidence supporting stringent therapy of this "negative x-ray

group" is less definitive.

SUMMARY

One hundred fifty-five cases of the peptic ulcer diathesis in young male United States Naval personnel are reviewed. One hundred eleven had radiologically demonstrable duodenal ulcer at some time during their illness, the remaining subjects comprising 18 cases with hyperchlorhydria alone, and 26 cases exhibiting radiologic duodenitis.

Similarity, and often identity, of clinical symptoms and signs were demonstrated among the three groups. Only diarrhea, nausea and vomiting were more prevalent among those without ulcers, whereas melena was more

common among the ulcer group.

Craters were more likely to be found in those whose symptoms began at an older age, in those with a longer clinical course, and in people smoking more than 10 cigarettes daily. Otherwise, no factors could be implicated as inducing formation of an ulcer crater.

Patients were observed to interchange among the three clinical stages during symptomatic exacerbations. The usual course was hyperchlorhydria, to duodenitis, to ulcer, the reverse path being traversed as the lesions healed

under standard treatment.

It is postulated that the different radiologic appearances correspond to three stages in a common pathophysiologic disease, the duodenal ulcer diathesis. In practice, patients with ulcer-like symptoms, showing hyperacidity by intubation and/or duodenitis on upper gastrointestinal series, should be treated as if a duodenal ulcer were present, even though no crater is visualized. It is likely that many of them will prove to have an ulcer if restudied during subsequent relapses.

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SUMMARIO IN INTERLINGUA

Es presentate un analyse de 155 casos de diathese pro ulcere peptic in juvene masculos del personal del Marina Statounitese. Omnes esseva symptomatic in le forma de (1) disconforto abdominal o (2) sanguination gastrointestinal. Cento e dece-un habeva un radiologicamente demonstrabile crater de ulcere e/o deformitate duodenal al un o al altere tempore in le curso de lor maladia. Le remanente gruppo "non-ulceric" consisteva de 18 casos de hyperchlorhydria e normal radiogrammas a barium e 26 casos de manifestationes radiologic de duodenitis.

Similitudes (e frequentemente mesmo identitate) del symptomas e signos clinic esseva notate inter le tres gruppos. Solmente diarrhea, nausea, e vomito esseva plus prevalente in le gruppos sin ulcere, durante que melena esseva plus commun in patientes ulceric. Tamen, grossier hemorrhagia gastrointestinal esseva observate in

approximativemente un tertio del subjectos in omne le gruppos.

Crateres esseva visualisate plus frequentemente in subjectos in qui le symptomas comenciava a un etate plus avantiate, in patientes con un plus longe curso clinic, e in individuos qui fumava plus que 10 cigarrettas per die. Nulle altere factores poteva esser incriminate como associate con crater ulceric o deformitate.

Esseva notate un transition del patientes inter le tres stadios clinic durante ex-

acerbation symptomatic. Le progresso usual esseva ab hyperchlorhydria via duodenitis a ulcere, e le direction opposite esseva observate durante le curation del lesiones sub le effecto de therapia standard.

Es postulate que le differente apparentias radiologic corresponde al tres stadios in un sol morbo pathophysiologic, le diathese pro ulcere duodenal. In le practica, patientes con symptomas ulceroide qui exhibi hyperaciditate in aspiration gastric e/o duodenitis in series supero-gastrointestinal deberea esser tractate como si ulcere duodenal esseva presente, mesmo si nulle crater o deformitate es visibile. Es opinate que multe tal patientes va revelar le presentia de ulcere si illes es studiate de novo al occasion de un recidiva subsequente.

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ECOLOGY OF SHIPS OF INNER SPACE*

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THE ecology of sealed chambers can be divided into three levels of selfsufficiency. There is the simplest level, that of sealing the subject or subjects in with some oxygen, some carbon dioxide absorbent, some food and water, and leaving them there as long as they can manage to survive. The second level may be described as partially regenerative. The food supply is finite, but the processes of providing oxygen, removing carbon dioxide, and providing water are regenerative and can continue indefinitely. In this system, waste is thrown away.

The third and highest level is that of the closed ecologic system. In such a system, the waste products are reprocessed into a useful form. Nitrogenous components of waste will form the basis of protein nutrient material. Exhaled and excreted water will be captured and purified for reuse. A mechanism which is the reverse of respiration is required to absorb carbon dioxide and to supply oxygen. Photosynthesis is such a mechanism, but as yet it has not been brought to a practical level of development. Toxic materials must be removed and immobilized or reprocessed.

Space ships of today, whether of inner or outer space, belong to one of the first two levels. The Diesel-powered submarine of World War II was of the first level, with finite limitations in several parameters. The nuclearpowered submarine soon will be of the second level. Its only important limiting parameter will be the food supply. Let us examine the elements of this partially regenerative space ship of inner space as it exists today.

WHAT THE NUCLEAR REACTOR DOES

The nuclear reactor makes available the energy within the atom to produce heat, which is useful, and ionizing radiation, which may be harmful. The heat released by fission is converted into a useful form as steam through intermediate heat exchangers. The steam is then utilized to provide the power to propel the ship and to generate electricity. The ionizing radiation released by a power reactor is dangerous, because the crew of the ship are not able to remain at a safe distance. Protective shielding around the reactor permits the crew to man watch stations in relative proximity without hazard.

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THE MARRIAGE OF THE SUBMARINE AND THE NUCLEAR REACTOR

The combination of the submarine and the nuclear reactor is a happy marriage, because each has something needed by the other. Of all the vehicles developed by man, the submarine is the only one in which added weight is not a disadvantage. The submarine needs added weight if it is to dive smartly and perform well as a submersible. Thus the added dead weight of the shield was not a disadvantage in the submarine. The nuclear reactor has the only kind of fuel available in useful form that does not require oxygen for the release of energy. This makes it possible for the submarine to remain submerged relatively indefinitely. There is no longer any necessity for the submarine to surface to charge the batteries for another dive. The nuclear reactor does not care whether the submarine is surfaced or submerged. The limiting factor in submarine operations today is the ability to provide a respirable, healthy atmosphere for the crew. The success with which this limitation has been removed is demonstrated by the 60-day, continuously submerged cruise of U. S. S. Seawolf. The most challenging problems of the moment are those of control of the atmosphere. The control of ionizing radiation is well in hand.

How SAFE IS THE REACTOR?

To the Port: The design of the reactor is such that it is safeguarded by both automatic and manual alarm systems and shut-off mechanisms. They are as safe as modern engineering designers can devise. The record of experience shows that, in the relatively land-locked river waters of the Port of New London, Connecticut, and the adjacent restricted waters of Long Island Sound, there has been no evidence of pollution or contamination of these waters by the products of ionizing radiation. There has been no evidence of any adverse effect on the balance of the marine ecology in this area. This is the record in the home port where U. S. S. Nautilus has been operating for four years, the U. S. S. Seawolf for three years, and the U. S. S. Skate for two years.

To the Crew: One of the triumphs of modern engineering has been the design of the shields of the nuclear reactors. This has made possible the practical application of this new source of energy. The record of experience shows that, on a nuclear-powered submarine, about 45% of the crew does not receive an exposure of sufficient magnitude to measure it with certainty with the instruments now available for this purpose. The dose these men receive is within the range of error of the instruments. Of the remainder of the crew, the man receiving the maximal exposure has not received a dose as great as 50% of the allowable annual dose rate. This is judging the subject from the strict annual permissible level of 5 rem set in 1956. This makes the success of the designer all the more dramatic, when it is understood that the reactor shields were designed at a time when the annual permissible dose rate was 15 rem. Experience has shown that nuclear reactors

are safe in a port area, do not contaminate harbor waters, and are safe to live with.

PROBLEMS OF ATMOSPHERIC CONTROL IN A NUCLEAR-POWERED SUBMARINE

When man is sealed in a chamber, everything is sealed in with him, and even his own metabolic processes must be suspected of having undesirable influences on his adequate function. An attitude of complacency, or a belief that the will can overcome all obstacles, is folly. Air contamination problems on the nuclear-powered submarines cover such diverse matters as: provision of oxygen, removal of metabolic by-products (such as carbon dioxide, methane), control of by-products of the habits of man, control of chemicals involved in environmental control, control of materials used in the machinery of the ship, control of materials used in construction and maintenance, control of the breakdown products of otherwise harmless materials, and interaction of trace materials.

In retrospect, it is understandable that most of these are not newly developed problems. For the most part, they are old matters that were of no importance in the days when a submarine could stay submerged only a matter of hours. It is the new parameter of long submergence, made possible by the anaerobic release of energy in the nuclear reactor, which has made these problems important today. An illustrative example of each problem will be cited in the material following.

Sources of Oxygen: Oxygen is made available from high-pressure storage flasks or is evolved by the combustion of certain chemicals. It will shortly be available from the sea.

Control of Metabolic By-Products: The most obvious of the metabolic by-products is carbon dioxide. It is removed in an air scrubber, using a regenerative chemical cycle. After the CO₂ is taken up it is given up in another phase of the cycle and pumped overboard. Then the chemical is available for another cycle through the scrubber. This has eliminated the chief difficulties encountered in the stowage of dry chemical absorbents.

An example of another metabolic by-product is the methane (sewer gas) formed in the sanitary tanks. While this is not a problem of any great magnitude at this time, the associated odors are removed on activated charcoal filters, and the methane is burned or absorbed in solution elsewhere.

Control of By-Products of Man's Habits: The most conspicuous example of this group is the production of carbon monoxide by tobacco smoking. Although this was known to be a consideration, it was of no consequence in the days of Diesel-snorkel submarines and the limitation of submerged cruising imposed by the storage battery. With indefinitely submerged cruises possible, this immediately became a problem of some consequence. Fortunately, a solution was at hand. Slight modification of a hydrogen burner, utilizing a catalytic hot-bed, now completes the combustion of carbon monoxide, and it is removed by the carbon dioxide scrubber.

Control of Chemicals Used in Environment Control: Two examples of this sort of problem are at hand. The chemical solution used in the carbon dioxide scrubber is itself irritant and toxic. If permitted to escape into the atmosphere, it would have undesirable effects on the crew. This imposed the necessity for designing a highly efficient removal device on the effluent end of the air flow channel. Temperature and humidity are maintained by air conditioning units using freon refrigerant units. Freon itself is regarded as a relatively safe gas, and is widely used in household refrigerators. The slow accumulation in the long-submerged submarine is a problem in a different context. However, there is another and even more important consideration, as we shall see later under "Control of the Breakdown Products."

Control of Materials Used in the Machinery of the Ship: The chemists have been very active during recent years in the development and introduction of new products for industrial application. Many of these new products meet highly restrictive demands in the area of physical characteristics. There has been a tendency to solve toxicologic implications by health engineering practices which minimize the hazard locally but add it to the overall burden of air pollution. Submarine designers wish to take advantage of these new developments in chemistry. But there is no external environment in which the submariner can dump his toxicologic hazard before the crew has been exposed. An example of such new developments has been a series of hydraulic fluids. Although they have been used widely in industry with relative impunity, toxicologic evaluation showed some of them to be entirely too toxic to consider for use in a submarine. On the other hand, a product known to contain a toxic ingredient demonstrated such physical characteristics as not to be a hazard to a submariner. In these instances the literature and experience of the manufacturer did not permit a proper decision regarding the usefulness of these materials aboard a submarine. Such experiences with hydraulic fluids have demonstrated the necessity for a toxicologic evaluation unit oriented to the quick development of information within the specific appropriate parameters of use.

Control of Materials Used in Construction and Maintenance of the Ship: Once the major problems were under control and longer submerged cruises were undertaken, other problems were brought into prominence. One of the first of these was the hydrocarbon burden of the air. Analytic methods revealed a situation so complex that efforts to identify individual hydrocarbons were abandoned. A broad attack by elimination and substitution was put into effect. One of the first measures taken was elimination of the old practice of submariners of cleaning ship by wiping it down with mineral spirits. "Mineral spirits" is a general term applicable to many petroleum-based paint solvents. While this custom was useful, and was no particular bother on the Diesel-powered submarines, it has no place on a nuclear-powered submarine. A considerable hydrocarbon burden persisted. Detective work revealed that, true to custom, the sailors would do a bit of surreptitious touch-up painting while submerged in spite of the directives

that had been written. This resulted in restrictions on painting, not only while at sea, but also during the period prior to departure on scheduled cruises. While this reduced the problem, a certain measure of this problem persisted. Further searching turned up such suspect items as linoleum adhesives, cigarette lighter fluid, glue in the hobby kits taken along for recreation, and other such minor items.

Control of the Breakdown Products of Otherwise Harmless Materials: Freon gas was mentioned above in relation to materials used in equipment controlling the atmosphere, and its generally good reputation was cited. This is all to the good, except that, once free in the ship, it is free to circulate through all the air treatment equipment. As it passes through the carbon monoxide burner, freon breaks down to give hydrochloric acid and hydrofluoric acid, both highly irritant to the eyes, nose and throat. Here we have an example of something which is relatively safe to live with which breaks down to something impossible to live with for any period of time.

Interaction of Trace Substances: A submarine is a complex mechanical and electrical installation. There are many electrical motors where ozone may be generated in trace quantities. There are many warm and hot surfaces where hydrocarbons can undergo chemical breakdown. Measurements of the particulate matter reveal a pattern of size and concentration comparable to a highly industrialized area ashore. This is understandable because, after all, no place on earth is more compactly industrialized than a submarine. An electrostatic precipitator is used to remove charged particles. This equipment has the potential of generating ozone. It is interesting to note that measurements of the inescapable air-borne radiation background that is everywhere can be used to check the efficiency of operation of the precipitator. This gives a clue to the thoroughness of the surveillance program aboard these ships. Just as one would expect, the oxides of nitrogen are present in trace quantities. One does not mention ozone or the oxides of nitrogen in a trivial way, because of their well known toxic potentials in low concentrations. It is in this field of the interaction of trace substances and their possible physiologic effects that submarine medicine and the study of air pollution stand together. Each has much to give and much to learn from the other.

PSYCHOLOGIC ATMOSPHERE

Submarine medical officers are repeatedly asked about the mental break-down rates among submariners. Lay groups, and even professional medical men, are often surprised to learn that the incidence of such problems is much less among submariners than in the rest of the military population. The submarine medical officer is soon able to achieve the relationship of a family doctor and confidant for the group with which he serves. This provides a readily available professional person, often regarded as a non-disciplinarian, to whom troubles may be ventilated with a measure of impunity. It is the observation of experienced submarine medical officers that

in spite of the severely restricted space, the crew soon sorts itself into several small social clusters. These clusters appear to congeal around some leader. The leaders can be recognized as possessing the same pattern of characteristics as the "leading citizens" of any small community. Each is an expert, at least in his own mind, in some field of human endeavor. At the beginning of a cruise these social clusters form within a few hours to a few days. They tell each other their stories and troubles until each one has given his all and has heard everything the others have to say. Gradually the groups break up, drift apart, and realign themselves anew and start all over again. It can be appreciated that, among 80 men, an enormous number of combinations of six or eight men is possible. Thus it takes quite a while for even a rather unpleasant person to inflict himself on everyone in the group.

With this understanding of the group dynamics of a submarine crew, and the realization that the group is composed entirely of volunteers who then are screened for latent undesirable characteristics, it is readily appreciated that the potential for mental aberration during a cruise is quite small. In addition, the circumstances of the operations are supportive, and the man can make it back to port, where he can quietly make his own way, or can be led, out of the submarine service.

For those interested in aspects of human behavior in terms of objectives and recognition, the submarine service is a most unusual laboratory. The nature of the selection process, the format of training, the relationships on board, all the way up to and even into retirement, provide a progressive series of valid, limited objectives leading toward the ultimate goal of an honored retired citizen with a fairly adequate income for life. The level in the military hierarchy to which a man may aspire through this service is an inspiration in itself. Numerous line officers with submarine experience have been promoted to the rank of Rear Admiral and Vice Admiral. A relatively high ratio of enlisted men achieve commissioned officer status.

SUMMARIO IN INTERLINGUA

Ill existe tres nivellos in le ecologia de cameras claudite, i.e. illos del statos (1) nonregeneratori, (2) partialmente regeneratori, e (3) completemente regeneratori. Usque 1955, naves esseva del prime de iste nivellos, tanto in le caso de naves terrestre como etiam in le caso de projicite naves del spatio cosmic. Le advento del potentia nucleari placiava le submarino al limine del secunde nivello. Tosto, submarinos va functionar plus o minus completemente intra le area correspondente a ille nivello. Le experientias colligite usque al tempore presente permitte delinear le natura e le complexitate del problemas que va esser sublevate per le ecologia completemente regeneratori (i.e., le ecologia a cyclo claudite) characteristic del astronaves futur.

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A CLINICAL, PHYSIOLOGIC AND PSYCHOLOGIC STUDY OF 20 GERIATRIC CLINIC PATIENTS *

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THE establishment of the Pearl Geriatric Clinic at the Peter Bent Brigham Hospital promoted a focus of interest on the ambulatory elderly patient within a separate clinic activity. At the outset it seemed desirable to undertake a comprehensive evaluation of those elderly individuals who became part of the clinic program, with its ancillary occupational and physical therapy services. Although minor physical complaints were often the basis for referral, most patients were seeking a long-term supportive relationship that would satisfy their various medical needs, whether physical or emotional. The study reported here was not designed as a statistical survey of the general geriatric population. Rather, it was intended to identify the characteristics of the individual who becomes a "Geriatric Clinic patient" in a university teaching hospital, situated in a heavily populated urban area. It was hoped that this would help to establish (1) what sort of information or measurement would be most useful in evaluating and classifying such a patient; (2) whether physiologic and psychologic capacities were interrelated or independent; (3) a better understanding of the so-called "aging process."

The individual studies reported were arbitrarily chosen on the basis of the most available technics and interests of the individual specialists performing them. No examiner was informed of his colleagues' evaluation of a given patient until completion of the study, in an attempt to keep the individual ratings as free from bias as possible.

METHOD

The members of the study team consisted of the clinic internist, neurologist, clinical psychologist, psychiatrist, pulmonary physiologist, social worker and nutritionist, A total of 20 patients were selected at random from the active geriatric clinic population (numbering approximately 120 patients), and were studied in detail, as outlined below. Other than the initial examination by the internist, the order of study did not necessarily conform to the order in the following list. No patient had more than two examinations in any one day.

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I. General Medical Evaluation:

- A. Internist's complete history and physical examinations, plus studies consisting of urinalysis, hematocrit, white blood count, differential smear, chest x-ray, electrocardiogram and cervical (Papanicolaou) smear during pelvic examinations in females; and audiograms, and visual acuity testing.
- B. Examination by the neurologist.
- C. Interview by nutritionist.

II. Physiologic Evaluation:

- A. Pulmonary function studies, which included measurement of the mechanical properties of the lungs and thorax.
- B. Study of the postural reflexes by use of tilt table, with continuous recording of electroencephalograms, plus serial blood pressure, pulse, and plasma catecholamine determinations.

III. Psychologic and Social Evaluation:

- A. Recorded interview with the psychiatrist.
- B. Testing by the psychologist.
- C. Interview with the social worker.

RESULTS AND COMMENTS

I. Medical Evaluation (table 1)

A. General: The sex ratio for the 20 subjects, characteristic of the overall Geriatric Clinic population, was one male to four females, with an age range of 64 to 81 years, averaging 72 years of age. All but two subjects had an important disorder, but none had an overwhelming disability. In five subjects the systolic pressure was 150 mm. Hg or above, and the diastolic 100 mm. Hg or below, which was consistent with the diagnosis of systolic hypertension on the basis of arteriosclerosis. In three subjects the systolic pressure was 190 mm. Hg or above, and the diastolic pressure was 100 mm. Hg or above, and in all three cardiomegaly was demonstrated by x-ray; in these instances the diagnosis of hypertensive cardiovascular disease was made. The most obese subject had a blood pressure of 190/110 mm. of Hg without cardiomegaly; a diagnosis of essential hypertension seemed justified.

In six subjects there was symptomatic osteoarthritis, proved by x-ray, of a moderate to severe degree. Subject M. D., with advanced malum coxae senilis, required crutches.

Deafness, defined as a hearing loss of above the critical level of 40 decibels at 4,000 cps in the better ear, was identified in seven subjects on audiometry. The tendency to a greater deficit at the higher frequencies in the absence of a demonstrable middle ear disorder in six of these subjects is consistent with the perceptual deafness of advancing years, "presbycusis."

The seventh subject, W. D., had marked hearing loss secondary to a severe conduction deafness from chronic bilateral otitis media. The finding of a greater decibel loss at 4,000 cps in the left ear over the right ear in 15 of the 20 subjects, for which we had no ready explanation, is of interest.

Visual acuity (after correction with glasses in 13 instances) was remarkably good for the entire group, with a reading poorer than 20/50 (Snelling eye chart) in the better eye in only one instance (W. D.). Lenticular opacification of minor degree accounted for these moderate degrees of decreased vision in most instances.

Obesity was the only other medical condition of a significant incidence (six cases), and in only one instance was it severe (L. B.). This diagnosis was applied to subjects with a weight of more than 20 pounds above the upper range of normal for age-height-sex as given in the Metropolitan Life Insurance Standard.²

Other isolated diagnoses are given in table 1. Medically, the group could be characterized as showing a significant tendency toward arteriosclerotic hypertension, osteoarthritis, presbycusis and obesity, without any overwhelming disability.

B. Neurologic Evaluation: The most common complaint was forgetfulness. This came as a spontaneous comment in eight subjects, and was easily elicited in six more on direct questioning. Almost all subjects agreed that with age there seemed to be increasing difficulty in recalling specific things, i.e., names and telephone numbers. Often a subject would not recall a well known fact when directly questioned, but could remember this information a few hours or a day later spontaneously and without prompting. It was noted that new tasks were now more difficult to master, and subjects would often boast about their remote memory to cover up defects in recent memory. Fourteen subjects had significant changes in formal mental testing (table 1) as tested by orientation to time, place and person, ability to name Presidents, serial 7's, numbers forward and backward, and response to the query, "What would you do if you were the first one in a theatre who saw a fire break out?" Judgment was deficient in eight subjects. None of the subjects would admit to defects in judgment, in contrast to their ready admission of difficulties with numbers. The test most commonly performed poorly was numbers forward and backward.

Four subjects gave a history of cerebrovascular episodes, mild and transient in three, though 10 subjects had localizing signs indicating some mild

damage to the pyramidal tracts at some time during their life.

Unsteadiness of gait was noted by five subjects. This was accounted for by evidence of old cerebrovascular disease in two, and by mild senile chorea in three. The choreic difficulty was manifested by unsteadiness of gait, often slightly wide-based and awkward, and finger movements which were especially noticeable when the subjects were walking; restlessness and facial mannerisms were other manifestations.

Clinical, Physiologic and Psychologic Data on the 20 Subjects TABLE 1

| Subject Age Sex | N N | Sex | Primary Disability | Blood | Audio Decib at 4,0 | Audiograms Decibel Loss at 4,000 cps | Vital | Rise in Pulse Rate on | 1.0. | Psychiatric Ranking | Mental Status* | Social | Rorschach |
|-----------------|-----|-------|--|---------|--------------------------|--------------------------------------|-------|-----------------------------|------|------------------------|-------------------|-----------|-----------|
| | | - (1) | | Bur ug | Rt. | Lt. | | | | | | | |
| | 95 | (1) | Psoriasis | 150/90 | 13 | 10 | 3.6 | 9 | 135 | Good | | Fair | |
| F. B. | 77 | ×, [2 | Osteoarthritis Hypertension due to arteriosclerosis | 210/90 | 20 | 89 | 1.68 | 00 | 288 | Poor | 3+ | Good | Senile |
| | 72 | 1 | Exogenous obesity | 190/110 | 81 | 20 | 1.20 | 00 | 114 | Excellent | | Excellent | |
| | 72 | M | Old cerebrovascular accident with | 140/80 | | 65 | 2.69 | 12 | 103 | Poor | ++ | Good | |
| W. D. | 73 | M | Chronic bilateral otitis media with | 160/80 | 80 | 95 | 2.9 | 12 | 95 | Fair | 7+ | Good | Senile |
| M. D. | 72 | [| Malum coxae senilis | 160/80 | 40 | 50 | 2.75 | 0 | 117 | Good | 2+ | Good | |
| E. F. | 71 | (L | Osteoarthritis and osteoporosis | 160/90 | 45 | 45 | 2.08 | 0 | 120 | Fair | +1 | Fair | Normal |
| i E | 78 | 1 | Osteoarthritis | 150/80 | 35 | 40 | 2.86 | 9 | 100 | Fair | 3+ | Excellent | |
| . F. | 11 | M | Senile chorea with ataxia | 190/100 | 8 | 8 | 3.62 | 0 | 101 | Good | 7 | Excellent | |
| M. G. | 69 | 1 | None | 160/80 | 10 | 13 | 1.90 | 9 | 116 | Good | +- | Excellent | Presenile |
| C. H. | 2 | M | None | 125/70 | 13 | 25 | 2.95 | 18 | 122 | Poor | 7+ | Fair | |
| M. K. | 75 | 1 | Cholesteatoma with draining chronic otitis media. left | 190/80 | 22 | (100) | 1.71 | 9 | 105 | Excellent | ++ | Excellent | Normal |
| | 89 | M | Varicose veins with varicose ulcers | 145/90 | | 95 | 3.59 | 0 | 110 | Fair | 7+ | Good | Presenile |
| S. M. | 99 | | Hypertensive cardiovascular disease | 240/110 | 35 | 20 | 2.04 | 9- | 100 | Fair | 1+ | Excellent | Presenile |
| | 73 | 7 | Hypertensive and arteriosclerotic | 230/120 | | 82 | 2.05 | 12 | 100 | Excellent | 7+ | Fair | Presenile |
| | | | mvocardial infarction | | | | | | | | | | |
| | 76 | 1 | Osteoarthritis | 150/100 | | 15 | 2.51 | 15 | 127 | Excellent | | Excellent | |
| | 89 | (T | Irritable colon | 160/95 | | 15 | 2.86 | 24 | 119 | Poor | | Poor | |
| S. R. | 71 | (24 | Hypertension due to arteriosclerosis | 190/90 | 35 | 35 | 1.60 | 18 | 86 | Poor | 3+ | Poor | Presenile |
| | 69 | 2 | Hypertensive cardiovascular disease | 200/120 | | 95 | 2.1 | 3 | 80 | Good | | Good | |

* Mental Status rating by neurologist.

0 = normal mental status.

= oriented x3; serial 7's slowly with less than 2 mistakes; digit retention—7 numbers forward + 5 numbers backward; judgment, good.

1 = oriented x3; serial 7's slowly with less than 4 mistakes; digit retention—7 numbers forward + 5 numbers backward; judgment, fair.

2 + = oriented x3; serial 7's poorly; digit retention—5 numbers forward + 3 numbers backward; judgment, fair.

3 + = oriented x2; serial 7's poorly; digit retention—4 numbers forward + 3 numbers backward; judgment, poor

4 + = oriented x1; serial 7's poorly or not at all; digit retention—4 numbers forward + 2 numbers backward; judgment, poor.

Numbness and paresthesia of the extremities were noted by six subjects. Evidence of a mild distal neuropathy or posterior column loss was noted in 12 patients. This was indicated by absent ankle jerks in four, vibration sense deficit in three, deficient vibratory and position sense in three, absent ankle jerks and deficient vibration sense in one, and absent ankle jerks with deficient vibration sense and position sense in one. Tremor was noted in two subjects, and this was a characteristic senile tremor of head, hands and adductors of the thighs. One subject had evidence of arteriosclerotic parkinsonism.

Pupils were noted to be between 1.5 mm. and 2.5 mm. in most subjects, which is consistent with the pupillary narrowing associated with aging. The reaction was sluggish in many. Defective upward gaze, sometimes

found in older age, was noted in five individuals.

Deficiency in muscle tone was difficult to evaluate or quantitate and, except for one patient with early parkinsonism, was felt to be within the range of normal in most patients. Some difficulty in relaxing muscles and coöperating in testing was noted in many subjects, identifiable as frontal

lobe rigidity associated with the aging process ("gegenhalten").

The findings encountered in this series are representative of most reported geriatric patient studies.⁸ The high incidence of senile chorea was impressive, and suggested that this may be a common cause of unsteadiness in the aged, though usually remaining unrecognized because of the lack of localizing neurologic findings and the nonspecificity of the choreic syndrome. Also of note was the failure of judgment in many of these patients, this being commonly regarded as remaining intact as one grows older.⁴ The high incidence of minor and nonspecific neurologic findings was notable in a randomly selected group such as this. This takes on added significance in the light of observations showing a 40% incidence of vascular lesions (hemorrhage or infarction) in brains examined in unselected patients dying after the age of 70.⁵

C. Nutrition Interview: The nutritionist employed a standard Nutrition Clinic history form which provided a review of "eating conditions" of the subjects, i.e., edention, bowel habits, finances and living arrangements, as well as a 24-hour recall of the food intake and a cross check by general food groups. The diets were calculated for calories, carbohydrate, protein, and mineral and vitamin content, using the "Food Composition Table for Short Dietary Analysis," and were compared with the National Research Council standards for men and women age 65 and over. The subject's weight was compared with the extremes given by the Metropolitan Life Insurance

tables.2

One subject lived in a boarding home where all meals were provided. The other 19 subjects lived in circumstances in which they were obliged to provide for their own meals, cooking for themselves, having them cooked in the home, or going to restaurants.

One subject (L. B.) was approximately 100 pounds overweight; two were 30 pounds and three were 20 pounds overweight; one subject (J. F.) was 20 pounds underweight. The remaining 13 subjects gave a history of a recent weight change to account for deviation from the ideal range.

A sedentary group such as this probably requires less than the 1,800 calories for females and 2,600 calories for males recommended by the National Research Council. The caloric range for the subjects was 1,274 to 3,040, with an average of 1,900. Subjects L. B., M. D. and A. Q. were considerably overweight and yet reported normal caloric intake, probably as a result of recent dietary instruction. Subject W. D. reported the highest caloric intake and was of normal weight. The only underweight subject (J. F.) was noted to be one of the most hyperkinetic of the group. Carbohydrate intake, ranging from 152 to 345 gm., was excessive in only one subject (S. M.), who was obese. Protein intake ranged from 65 to 114 gm. in the males (recommended allowance, 65 gm.), and from 50 to 119 gm. in the females. Only one subject (A. D.) received less than the recommended allowance.

Two subjects reported a mildly deficient calcium intake, and in eight it was 75% or more above the recommended level, correlating fairly well with milk-drinking habits. Iron intake was mildly to moderately deficient in four subjects (all females); subject E. B. had previously been treated for a severe anemia secondary to a deficiency of dietary iron.

Six subjects reported diets containing less than the recommended 5,000 units of vitamin A. Subject M. D. was the most deficient, reporting 1,300 units, due to her use of skimmed milk, low butter or margarine intake, and lack of adequate intake of fruits, vegetables and eggs. Six subjects reported an inadequate intake of ascorbic acid, ranging from 25 to 75% below the recommended requirement, correlating with a poor intake of citrus fruit. Eight subjects reported an inadequate intake of thiamine (25 to 50% below recommended requirement), which correlated with a poor intake of whole grain and enriched products. Riboflavin intake was adequate in all instances, correlating with a generally good intake of meat. Niacin intake was inadequate in only two instances.

A tendency to a mild to moderate deficiency of dietary vitamins was the most striking nutritional finding for the group.

II. Physiologic Evaluation

A. Pulmonary Function Studies: Studies of respiratory function of these 20 subjects included determinations of vital capacity, maximal breathing capacity, and pulmonary airflow resistance and compliance * by a method previously described. During the measurements of compliance, maximal inspiratory pressure was recorded in each instance. All patients were

^{*}An expression of the elastic characteristics of the lungs and thorax expressed in liters volume inflation per centimeter H₃O transpulmonary pressure developed.

studied during quiet, spontaneous respiration in the sitting position. The general procedure was explained to each subject with care so that maximal coöperation would be obtained.

Vital capacity was reduced below the predicted value (based on height and age) in 15 of the 20 subjects (table 1). No subject demonstrated an abnormal pulmonary compliance; all fell within the normal range of 0.10 to 0.30 L./cm. H_2O pressure. Pulmonary airflow resistance was normal in all but three of the subjects, and in these three the resistance was slightly above the upper limit of normal. The maximal negative inspiratory pressure attained normal ranges in only two of the 20 subjects. In all the others it was less negative (range -7 to -23 cm. H_2O) than the range for normal young subjects (-25 to -35 cm. H_2O). The resting end expiratory pressures were in the normal (negative) range in all but two subjects, in whom it was positive at +1 and +4 cm. H_2O . One of these two (M. G.)

also had a significantly elevated airway resistance.

Studies of pulmonary function on older individuals have been reported previously by various authors. 10-15 In general, these other authors found a slight reduction in the vital capacity (VC), with a corresponding increase above the normal of the residual volume (RV). The total lung capacity (TLC), which is a combination of the residual volume and the vital capacity, was therefore normal, but the ratio of these two major compartments (VC/RV) was altered. More commonly, this volume alteration is expressed as the ratio of the residual volume to total lung capacity. The normal range is from 20% to 40%. In these older subjects this ratio was generally in the range of 40% as compared with the findings in patients with emphysema of 50% to 60%. The mechanical behavior of the lungs of elderly subjects has been shown to be qualitatively similar to that observed in emphysema.10 Again, as in emphysema, gas distribution has been found to be slightly impaired in the older subjects. 10 Similarly, a study of these same factors in 28 healthy older subjects 15 revealed a slightly (but insignificantly) lower pulmonary compliance in the elderly subjects in comparison with healthy young adults. Pulmonary airflow resistance was slightly (but insignificantly) higher in the older subjects. There was, however, a significant difference between the young and old subjects in the maximal negative inspiratory pressure that could be developed. In the younger group the values ranged from -21.5 to -45.0 cm. H₂O, and in the older group from - 12.5 to - 37.0 cm. H₂O. Total lung capacity was not significantly different between the two groups. This loss of ability in old age to develop maximal negative inspiratory pressure as reported by Frank et al. 15 was the most consistent and striking change in the studies reported here. In six patients with advanced emphysema, Mead et al.9 found the maximal inspiratory pressure to be similarly reduced, ranging from -7 to -11 cm. H₂O.

In summary, in the ambulatory elderly subject there was a slight to moderate decrease in pulmonary function which, as noted in earlier studies,

bears a qualitative similarity to the changes seen in emphysema, and may be due to slight changes in the visco-elastic properties of the lungs and thorax.

B. Tilt Table Study: To evaluate the peripheral and neurovascular adequacy of the subjects under an orthostatic stress, each subject was placed horizontally on a tilt table for a 30-minute control period and then tilted upright to 60° for a 30-minute period. Continuous six-channel electroencephalographic recordings and Lead V4 electrocardiographic recordings were made. Serial blood pressure recordings were taken from the left arm with a standard aneroid blood pressure cuff. Venous blood samples were drawn from the patient's right arm during the control period, and at two and one-half, five, 10, 20 and 30 minutes after tilting upright. The plasma was subsequently analyzed for concentration of epinephrine and nor-epinephrine by the Aronow and Howard modification 16 of the Weil-Malherbe and Bone

TABLE 2
Tilt-Table Data

| | | in B.P. | | 1 | ohrinet | Norepin | ephrine‡ |
|------------------------------------|-----------------|------------------|--|---|---|---|---|
| | Syst. mm. Hg | Diast. mm. Hg | Rise in Pulse on Tilting* bents/min. | Increment on Tilting µg/L. plasma | Time to Reach Peak after Tilt min. | Increment on Tilting µg/L, plasma | Time to Reach Peak after Tilt min. |
| Average | -12 | 3 | 8 | 0.3 | 11'§ | 1.2 | 17' |
| Average for 6 young controls | - 5 | 12 | 19 | 1.0 | 8′ | 2.3 | 8' |

^{*} Between control value just prior to tilt and value at point of peak norepinephrine level after tilt. In subjects without rise in NE, the point at 10' after tilt is taken.

Average for the 7 subjects (39%) who showed significant rise.

Average for the 14 subjects (78%) who showed significant rise.

method.¹⁷ Previous studies from this laboratory have shown a significant increase in the plasma concentration of epinephrine and norepinephrine in response to the tilt stress. The physiologic background and a detailed description of the methodology and results of this procedure are described in an earlier report.¹⁸

Table 2 compares the average for the hemodynamic and catechtolamine responses in the 20 subjects with the average changes for six young control subjects (age 15 to 34) previously studied in this laboratory in identical fashion.¹⁸ The changes in blood pressure and pulse recorded were the difference between the level recorded at the end of the control period prior to the tilt and the level recorded following the tilt at the time of the peak rise in plasma norepinephrine concentration (ranging from 2.5 to 30 minutes of tilt).

[†] Epinephrine—normal range: 0-1.5 μ g/L. plasma (all subjects had control values within this range).

[‡] Norepinephrine—normal range: $1.0-5.5~\mu g/L$. plasma (all subjects had control values within this range).

The 20 subjects showed an average systolic fall of 12 mm. Hg, as compared with 5 mm. Hg for the young control group. They showed an average diastolic rise of 3 mm. Hg as compared with 12 mm. Hg for the young control subjects. The average pulse rise was only eight beats per minute, as compared with 19 for the younger group. Table 1 shows the

individual pulse rate changes.

The mean peak level of plasma epinephrine following tilting was not significantly different from the mean level determined during the control period. However, the difference between mean control and peak nor-epinephrine levels was of probable significance.* This is in contrast to the young control group, which showed a highly significant rise in both epinephrine and norepinephrine after tilting. In the seven elderly subjects who showed a rise in the epinephrine level of 0.4 µg./L. plasma or above, the average time following the tilt to the peak level was 11 minutes, as compared with eight minutes for the young group. The average time elapsing between the tilt and the peak norepinephrine in the 14 elderly subjects who showed a rise of 0.8 µg./L. plasma or above was 17 minutes, as compared with eight minutes for the young control group.

There was only one incident of vasovagal fainting in the 20 subjects on tilting upright (M. K.), a 5% incidence; the incidence of vasovagal fainting in a large series of young subjects on tilting upright has been given at

20%.10

The only subject (E. B.) who showed electroencephalographic changes that could not be considered "normal for the age" developed left frontal and parietal slowing after 15 minutes of tilting, diagnostic of a cerebrovascular insufficiency syndrome. The demonstration of electroencephalographic slowing over an area of preëxisting cerebrovascular disease depends upon a significant fall in blood pressure (and cerebral blood flow) on tilting, as previously reported. Since only one of the subjects showed a hypotensive response to tilting (M. K. who fainted after 30 minutes of tilt), the failure to demonstrate more electroencephalographic abnormalities is understandable.

In general, the older subjects showed a less vigorous hemodynamic response and a diminished autonomic lability as compared with the young subjects in terms of blood pressure, pulse, catecholamine responses, and incidence of vasovagal syncope. A diminished autonomic lability in the aged could be considered to be evidence of diminished adaptability to sudden environmental changes. Given a stable environment; however, this might be an advantage in the elderly individual in terms of a relative freedom from abrupt changes in his internal environment.

III. Psychologic and Social Evaluation

A. Psychiatric Data: The psychiatrist had two general aims: (1) to evaluate a representative sample of 20 patients from the Geriatric Clinic,

^{*} Significance determined by Fisher's "t" test.

and (2) to characterize the findings in such a way that personality structure could be correlated with data obtained by other methods, including physiologic and psychologic tests. An initial evaluation was made on the basis of a single interview, which was recorded and transcribed. When the interviews were completed, all 20 records were reviewed and evaluated again to obtain the range of individual variation in the capacity for effective adjustment in old age. Since these were normal subjects, defined as patients who had not been referred for specific psychiatric problems, each subject was compared with all other subjects in the group. These comparative evalua-

TABLE 3 Psychologic Performance Rating*

| Subject | Mental Status, Rating by Neurologist | Psychiatric Rating | Social Service Rating | Rorschach Rating | | |
|----------------|--|--------------------|--------------------------|------------------|--|--|
| S. B. | -1 | 0 | 0 | +1 | | |
| E. B. | -1 | -1 | +1 | -1 | | |
| F. B. | -1 | +1 | 0 | 0 | | |
| L. B. | +1 | +1 | +1 | 0 | | |
| F. D. | -1 | -1 | 0 | -1 | | |
| W. D. | 0 | 0 | - 0 | -1 | | |
| M. D. | 0, | 0 | 0 | 0 | | |
| E. F. | +1 | 0 | 0 | +1 | | |
| C. F. | -1 | 0 | +1 | 0 | | |
| J. K. | 0 | 0 | +1 | -1 | | |
| M. G. | +1 | 0 | +1 | 0 | | |
| С. Н. | 0 | -1 | 0 | +1 | | |
| M. K. | +1 | +1 | +1 | +1 | | |
| E. M. | 0 | 0 | 0 | 0 | | |
| S. M. | +1 | 0 | +1 | 0 | | |
| M. N. | . 0 | +1 | 0 | 0 | | |
| B. P. | +1 | +1 | +1 | +1 | | |
| A. Q. | - | | | 0 | | |
| S. Ř. A. W. | -1 | -1 | -1 | 0 | | |

* +1 = "Excellent" rating by psychiatrist and social worker, "Normal Aging" response on Rorschach and ± to 1+ deficiency on mental status examination.

0 = Fair to good rating by psychiatrist and social worker, "Presenile" response on Rorschach, and a 2+ deficiency on mental status examination.

-1 = Poor rating by psychiatrist and social worker, "Senile" response on Rorschach, and a 3+ to 4+ deficiency on mental status examination.

tions were ranked from 1 to 20, on the basis of personality effectiveness, and subdivided into approximate subgroups as excellent, good, fair and poor (table 1). This procedure provided an empiric classification that was consistent for the 20 subjects studied, without the necessity of establishing a hypothetic standard for "normal" aging. An attempt was made to estimate the interrelationship between the innate capacity for adaptation and the influence of external events, including favorable life situations and the occurrence of bereavement, economic loss and physical disability. Although sharp distinctions were often difficult to make, and early events modified the capacity to adapt, two general types of reaction to adverse experience could be recognized in early childhood that tended to recur throughout adult life and into old age. One type may be characterized as a pattern of enhanced adaptive functioning, in which the individual responds to emotional loss or physical impairment by mastering the experience and making the maximal use of his abilities. The other type may be called a regressive reaction, in which the individual responds to adverse experience by surrendering certain potential capacities and reëstablishing an equilibrium on a lower level. Although these types represent extremes, and most patterns include both tendencies, one tendency may predominate, and some individuals seem to mature in response to adverse experience, while others cease to develop, or return to immature patterns of adaptation.

On the basis of these limited psychiatric observations on selected volunteer subjects, the factors influencing effective adaptation to normal aging

may be summarized in the following general impressions:

1. The influence of age itself, and its physical or intellectual impairments, was less important than was the continuity of certain consistent personality patterns that could be recognized throughout the subject's life. A quality which may be called maturity or ego-strength became apparent early in childhood, was reflected in a characteristic manner of handling subsequent conflicts, and determined the effectiveness of the subject's adaptation to the vicissitudes of aging.

2. This quality was chiefly related to the maturity of the subject's early relations with his parents, which influenced his lifelong capacity to establish dependable relationships with others. The more satisfying his original family attachments, the greater the subject's ability to tolerate the progressive loss of significant relationships with advancing years, and to find ef-

fective emotional substitutes.

3. Certain personality functions had a special importance throughout the lives of each subject: characteristic patterns of obtaining satisfaction through physical activity, intellectual or manual skills, and the uses of memory, perception and communication. The greater its emotional importance in early life, the better preserved this particular function tended to be in old age.

4. The most effective subjects had dealt successfully with separation and loss of significant figures during adolescence or later. The least effective subjects had lost parents in early childhood (C. H.), had never freed themselves from an early dependence (F. D.) on their family relationships, without unusual experiences of separation or loss, were isolated and lacking in closeness (A. Q.). The least effective subjects developed neurotic symptoms in response to retirement, or showed a strong tendency toward depressive reactions.

5. Aging and death are intrinsic phases of biologic development, not merely the results of accumulated pathophysiologic accidents. The process of aging seems to be influenced by the individual's capacity to maintain con-

tact with meaningful sources of emotional satisfaction, through personal relationships, physical activities and intellectual interests.

B. Psychologic Tests: To establish a comprehensive picture of the geriatric patient's intellectual, perceptual and emotional functioning, a variety of tests was employed. These included a Rorschach test, an intelligence test (short form of Wechsler-Bellevue scale), visual memory test, flicker fusion thresholds,* time sense studies, and a speed-of-reading procedure. Instructions were conveyed clearly to subjects with impaired hearing so that a poor performance could not be attributed to failure to hear the instructions.

The intelligence scores ranged from 80 to 135, with a mean intelligence quotient (I. Q.) of 107. Practically all subjects revealed a marked reduction in the separate subtests which are expected to detect intellectual impairments. Recall of past material was more effective than was immediate recall; sensory-motor speed was reduced and, most significantly, the performance on the Block Design Test † was consistent with the kind of intellectual impairment found in brain-damage patients. On the Block Design Test, five subjects used yellow blocks quite interchangeably with white ones, as if they had lost the power to discriminate yellow from white.

Practically all scores on the separate intellectual functions of the intelligence test were below expectation if the vocabulary level is taken as an index of original capacity. Thus, the discrepancy between actual I.Q. and theoretic I.Q.‡ revealed a mean loss of 12 points, with a range of 0 to 32 points.

The speed-of-reading procedure required the subjects to read a list of 100 color words (red, green, yellow, blue, printed in large type) arranged in 10 rows. When the time to read this list was correlated with intelligence score, the resulting correlation (0.62) was significant. Thus, a simple procedure, measuring speed of reading and requiring no comprehension, could be used to predict with good accuracy the subject's over-all score.

Another sensory-motor test, the Digit Symbol test, revealed an even higher predictive correlation. In this test the subject was required to associate symbols with numbers; both speed and accuracy of his performance were recorded. In a normal population this test correlates 0.70 with actual I.Q.²⁰ In this group the correlation was almost perfect at 0.99. It is said that speed of functioning is lost out of proportion to other mental functions with aging,²¹ but these findings indicate that with the loss of speed the other mental functions are proportionately reduced. These observations suggest that the best index of over-all intellectual competency in old age is the test that measures the speed of sensory and motor integration, whether in writing or speech tasks.

^{*}The frequency at which the eye can no longer detect the flickering of the light source. †The Block Design Test requires that the patient duplicate a complex design with colored blocks. It is a good measure of nonverbal intelligence, and sensitively reflects brain damage.

[‡]Theoretic I.Q. is defined as the peak I.Q. prior to decline with age, and is based on vocabulary capacity, which shows little if any change on aging compared with the other parameters of intellectual function.²⁰

The personality test data were evaluated so as to provide a useful classification of this geriatric population. The Rorschach is primarily thought of as a personality test,22 but it has also been used as an aid in diagnosing intracranial pathology.28 The recent work of Ames et al.24 moreover, demonstrated that a geriatric group could be classified according to "Normal Aging," "Presenile" or "Senile" * using Rorschach quantitative and qualitative signs established by the authors on a group of 200 old people. Our 20 subjects were classified by these criteria (table 1), and it was found that the Rorschach records could readily be grouped into these categories. The three groups ("Normal," "Presenile" and "Senile") represented increasing degrees of reduced responsiveness to outside stimuli, progressive impoverishment of associations, feelings and emotions, and progressive limitation of interest and flexibility. The Rorschach reactions resembled those of childhood of progressively lower ages when the "Presenile" and "Senile" groups were compared with the "Normal" aging group.

An analysis of the independent characteristics of these three groups revealed that age was not a factor in the differences found, although the mean age increased slightly with poorer test performance. The amount of loss in intelligence appeared to be important only for the "Senile" group. Education and actual I.O., however, were distinctly different from group to group. Thus, the lower the intelligence and the less the educational achievement, the more likely that the subjects would be classed as "Presenile" or

"Senile."

In our series, therefore, the higher the education and the more effective the intellectual performance of the subjects, the less the chance that emotional impoverishment and restriction would be found in the Rorschach examination. One can speculate that subjects with higher education have maintained an active interest in intellectual matters, and intellectual restriction has not taken place through disuse. It is important to note that the I.Q. scores and education for this group were below those of very superior or gifted individuals. Other studies 25 have shown this preservation of intellectual efficiency with aging in exceptionally intelligent people; our findings confirm this concept and extend its application to average ranges of education and intelligence.

C. Social Service Data: The social worker interviewed each subject, obtaining information that would permit a rating of the individual in terms of relative effectiveness of social adjustment. She was not directly concerned with intellectual function, personality structure or chronologic age. Although these factors were taken into consideration, it was more important from a casework point of view to estimate the subject's self-evaluation of his

present life situation.

This was a fairly regional group, in that 17 of the 20 subjects had been

^{*}These are arbitrary designations and are not meant to convey meanings beyond that of increasing difficulty in coping with the test and incidence of psychopathologic factors and reactions.

born in New England or the Canadian Maritime Provinces; only two were European immigrants. Twelve were Roman Catholic, seven were Protestant and one was Jewish. The male parent's occupation was generally farming, laboring or clerical. Educational achievement went beyond high school in six instances, but none was a college graduate. Social isolation was notable in that six were single, eight were widowed and two were divorced; only four were living with spouse. Of these 16 without partners, nine lived alone and six lived with relatives. Only two lived in their own homes; 17 lived in a furnished room or apartment; and only one was in a domiciliary situation (a home for the aged). In general, it would seem characteristic of this group that a degree of independence was preserved at the price of relative isolation. Also characteristic was the subsistence on marginal incomes: small savings and pensions, Old Age Assistance and Social Security. Only two were gainfully employed and lived on their current earnings. Previous employment for both male and female subjects was similar to that of the parents, being laboring or clerical.

The utilization of excess leisure time was an important problem for the entire group. The manner in which this was solved gave the best indication of the subject's degree of satisfaction with his present social situation. Some subjects led full lives, busily participating in such activities as adult education courses, organized club and church groups, fishing trips, gardening and painting. At the other extreme were those subjects who rarely left their apartments, and spent their days watching television, doing a little housework, sewing or reading. The degree of contentment expressed by the subjects was proportional to their ability to keep physically active and to enjoy a range of creative interests. Largely on this basis, the social worker was able to give a relative rating of general social adjustment as follows: excellent in seven, good in six, fair in five, and poor in two of the 20 subjects. Table 1 lists the rating for the individual subjects.

DISCUSSION AND GENERAL CORRELATIONS

Analysis of the results revealed correlations within two broad areas: the clinical and physiologic on the one hand, and the psychiatric and social on the other. The former correlated with the psychologic data pertaining to purely intellectual function (notably I.Q. score). The Rorschach test interpretations, sensitive to both organic brain deterioration and quality of emotional response, correlated with both. The mental status test on neurologic examination, which evaluated intellectual function, judgment and emotional status, correlated best with the psychiatric and social data. Nutritional data failed to correlate with any of the other data. Clinical and physiologic data showed a clear-cut relationship to chronologic age; psychiatric, social and mental status data seemed to be independent of age in this group. Within the age range studied, the absence of correlation between these two general areas indicates the existence of age-related and non-age-related variables.

Clinical, Physiologic and Intellectual Correlations: Correlations were made by selecting subjects at the extremes of a given test performance in order to emphasize the differences. Subjects rated according to extremes of hearing loss on audiometry gave the best correlations with adequacy of performance in other tests. Six subjects had a hearing deficit of 50 decibels or more,* and five subjects of 15 decibels or less, and these two extremes were compared with respect to systolic blood pressure, I.Q., age in years, Rorschach classification ("Normal Aging," "Presenile" and "Senile"), rise

FACTORS ASSOCIATED WITH PRESBYCUSIS

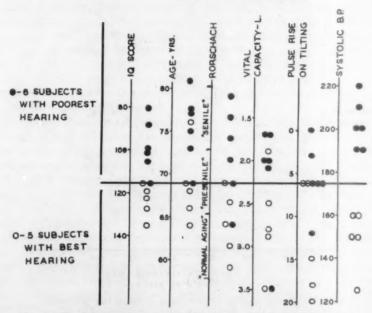


Fig. 1. Physiologic and psychologic factors associated with presbycusis.

in heart rate on tilting, and vital capacity. The results are shown graphically in figure 1. In general, it would seem that an aged individual with relatively severe presbycusis will tend to show a more advanced age, systolic hypertension and a "Presenile" or "Senile" Rorschach classification, as well as restriction of I.Q., vital capacity and pulse rise in response to an orthostatic stress. It is emphasized that instructions were clearly conveyed to the subjects, and a poor I.Q. or Rorschach rating was not related to failure to understand the instructions because of poor hearing.

When a comparison is made on the basis of the five oldest and the five youngest subjects, rather than on the basis of hearing loss, a similar trend

^{*}Subject W. D. was excluded because his hearing deficit was on a conduction basis.

is noted, but there is more overlap of results, and the mean differences in the same parameters are less impressive. Therefore, while age per se is a factor, the differences cannot be explained purely on the basis of age. The mean age difference between the extremes grouped according to auditory acuity, was only five years, whereas there was a mean difference of 12 years when the five oldest and the five youngest were compared. Decreased auditory acuity, vital capacity and I.Q. are well established phenomena of the "aging process." ²⁸ The age range of our subjects was too narrow, however, to account wholly for the extreme differences found in these studies. Thus, it seems likely that such extremes in performances within

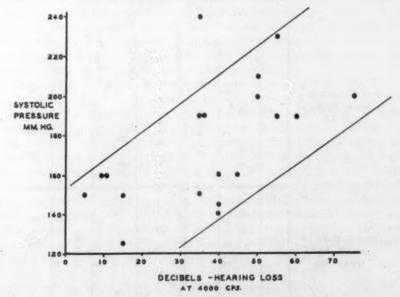


Fig. 2. Relationship of systolic blood pressure and presbycusis.

a relatively narrow age range are constitutionally determined, and that increasing age exaggerates these constitutional differences. Apparently, a constitutional tendency toward severe presbycusis is associated with a predisposition to other types of impairment.

Since systolic hypertension generally implies arteriosclerotic vascular disease, and the hearing loss is perceptual in type, the possibility must be considered that vascular disease could be related to development of this type of deafness. When systolic blood pressure was plotted against hearing loss for the group of 20 subjects (excepting W. D., with severe conduction deafness), a direct relationship was obtained (figure 2). However, a similar relationship between systolic blood pressure and flicker fusion threshold,

actual I.Q. and I.Q. loss was not found. It therefore seems appropriate to consider that hearing loss and systolic hypertension are both manifestations of some common constitutional factor, rather than to postulate a causal relationship.

The sensory deprivation resulting from presbycusis suggests another hypothesis. Perhaps a reduced intake of sensory stimuli lowers the level of cortical responsiveness and accounts for the intellectual impairment (I.Q. score) and emotional impoverishment observed with the Rorschach. The work of Hebb and many others recently reviewed by Solomon et al.²⁷ supports this hypothesis. The subject (W. D.) with the poorest hearing and vision in the entire group was the only subject rated clinically senile by the internist doing the general medical evaluation. A third hypothesis that deserves consideration is the possibility that selective need for or continued use of certain perceptual and intellectual functions prolongs or enhances their functional usefulness. Observations in prisoners of war, in whom prolonged disuse was associated with impaired intellectual and emotional functioning,²⁸ suggest such an explanation. The effect of sensory and social stimulation on the over-all function of the geriatric patient is an important area for further investigation.

Psychologic and Social Considerations: A comparison was made of the independent evaluations by the psychiatrist, neurologist, psychologist and social worker. The psychiatrist rated the subjects in terms of effectiveness of adjustment in old age on the basis of history and interview. The social worker rated them according to social history, emphasizing the subject's selfevaluation of his own life situation. The psychologist rated them on the basis of Ames's 24 categorization of the Rorschach record as "Normal Aging," "Presenile" and "Senile." The neurologist rated them according to his mental status examination. The ratings of these four examiners (table 1) were made comparable; the results are given in table 2. In four instances there was perfect agreement; in eight instances, good agreement (three examiners rated identically), and in three instances, fair agreement (two examiners rated just above or just below the other two). Thus, there was a fair to perfect correlation in the scoring of 15 of the 20 subjects. This degree of agreement is of importance, since the examiners were evaluating the subjects from the standpoint of such different disciplines. The probability of obtaining this agreement on the basis of pure chance was less than 1%.* Of the 15 subjects in whom there was fairly close agreement, three received a good rating, four a poor rating, and eight an intermediate rating in terms of psychologic and social adjustment and mental status. An analysis of the "leisure time" activities, as determined by the social worker, revealed a relative restriction of interests, capacity for hobbies and other avenues for creative outlets when the "poor" group was contrasted with the "good." An analysis for any correlation between these extremes in psycho-

^{*} On the basis of the Chi square test of significance and probability theory.

logic and social adjustment with the clinical and physiologic parameters, previously discussed, including chronologic age, was undertaken. The result was singularly striking in the total absence of even a rough correlation with any one of these factors.

The lack of agreement in the rating of five subjects was a finding that required analysis. In four of the five, the discrepancy was due to the neurologist's low rating of mental status, and the social worker's high rating of social adjustment, a finding highly unlikely by chance alone, as indicated by a statistical analysis. The neurologist measured specific parameters of mental performance, whereas the social worker estimated social adjustment and emphasized the individual's self-evaluation. Thus, a subject could show poor judgment response on mental status testing, yet the social worker could find that he or she was quite content, living alone in an apartment on Old Age Assistance.

The fifth subject (C. H.), on whom there was lack of agreement, illustrated another type of divergence. While the psychiatrist found a pattern of depression, impoverishment of interests and emotional relationships, and a certain lack of adaptability to change, the psychologist rated him "Normal Aging" on Rorschach; he had the third highest I.Q. score at 122, with no loss in I.Q., and was one of two subjects earning a salary at the time of this study. While the Rorschach material showed emotional impoverishment as found by the psychiatrist, this was not shown to be an age-related change, and he still rated a "Normal Aging" classification by the psychologist.

In brief, there was a statistically significant agreement in rating the majority of subjects, although each of the four evaluations was concerned with a different aspect of the individual. The neurologist and psychologist evaluated the sensorium but included nonintellectual factors, such as the influence of anxiety and depression. The social worker was not directly concerned with intellectual performance, but emphasized the individual's conscious attitudes and his self-evaluation of his own adjustment. The psychiatrist attempted to exclude the influence of intellectual deficits in evaluating the individual's lifelong pattern of personality functioning.

SUMMARY AND CONCLUSIONS

Twenty Geriatric Clinic patients were selected at random for a comprehensive evaluation. Findings that developed from correlations between the separate parts of the study were considered to be the most valuable aspect of the work, and may be summarized as follows:

1. Certain physical, intellectual and physiologic deficits tended to coexist in the same elderly individuals. When the subjects with pronounced presbycusis and normal hearing were compared, a striking tendency was found in the former to comparatively severe systolic hypertension, lower I.Q., diminished vital capacity and limited pulse rise on tilting upright. Chrono-

logic age was greater in the deaf group but could not account for the magnitude of the differences found within the relatively narrow age range encompassed by the study. This suggests that constitutional endowment is an important determinant in the occurrence and severity of coexistent late-

life deficiencies commonly associated with the "aging process."

2. In the four independent evaluations of mental function by the psychiatrist, neurologist, social worker and psychologist there was a statistically significant similarity in the ratings given the individual subjects. Individual differences in effectiveness did not correlate with chronologic age, intelligence level, and physical or physiologic impairment. The important determinants were (a) a lifelong pattern of successful adaptation to change, (b) dependable early parental attitudes and the capacity to establish successful personal relationships in later life, (c) educational achievement and maturity of emotional response, (d) ability to keep physically active or to enjoy a range of creative interests, and (e) preservation of memory and judgment. This suggests that one method of rating elderly individuals and defining their mental aptitudes might be based on a concept of over-all psychologic and social effectiveness.

3. A comprehensive evaluation of the ambulatory elderly patient will differentiate (a) age-related, constitutionally determined physical and physical changes, and (b) lifelong psychologic and social patterns. Further research on aging is particularly well suited to a comprehensive, correlative approach, including clinical, physiologic and psychologic methods. Such an investigation can be well carried out as part of a geriatric clinic devoted to a long-term treatment program.

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SUMMARIO IN INTERLINGUA

Es presentate un evalutation comprehensive de 20 patientes ambulatori de etates avantiate qui esseva attendite in le novemente establite Servicio de Clinica Geriatric in un hospital de instruction hospitalari. Le evalutation includeva aspectos clinic, physiologic, psychologic, e social. Le patientes includite esseva seligite al hasardo. Le objectivo del studio esseva establir (1) qual typo de information o de mesuration es le plus utile in le evalutation e classification de tal patientes, (2) si le capacitates physiologic e psychologic in illes es interrelationate o independente, e (3) un meliorate comprension del si-appellate processo de invetulation.

Esseva opinate que certe constatationes resultante del correlation inter le separate partes del studio esseva su plus significative aspectos. Illos pote esser summarisate

sequentemente.

1. Certe deficits physic, intellectual, e physiologic monstrava le tendentia de coexister in le mesme subjecto de etate avantiate. Quando le subjectos con grados sever de presbyacusia esseva comparate con le subjectos con acusia normal, il esseva

trovate que le prime de iste duo gruppos exhibiva un tendentia pronunciate de hypertension, reduction del quotiente de intelligentia, diminution del capacitate vital, e restriction del acceleration del pulso post le transition del corpore ab le postura horizontal a un inclination de 60 grados. Le etate chronologic esseva plus alte in le gruppo surde, sed iste differentia non sufficeva pro explicar le magnitude del differentias in le altere parametros mentionate, proque le etates del patientes includite in le studio non divergeva grandemente. Isto pare indicar que le dotation constitutional es un importante factor in determinar le occurrentia e le severitate del coexistente deficientias de etate avantiate que es communmente associate con le "processo del invetulation."

2. In le quatro independente evalutationes del function mental per (a) le psychiatro, (b) le neurologo, (c) le experto de assistentia social, e (d) le psychologo, il emergeva un statisticamente significative similaritate del predicatos attribuite al subjectos individual. Differentias individual de efficacia non se correlationava con le etate chronologic, le nivello del intelligentia, e le defectos physic o physiologic. Le importante factores determinatori esseva (a) un tradition ab le comenciamento del vita de successo in le adaptation a nove situationes, (b) constantia del attitudes parental durante le precoce phases del vita, e le capacitate de establir satisfacente relationes personal durante le subsequente phases del vita, (c) attingimentos educational e maturitate del responsas emotional, (d) le capacitate de tener se physicamente active e de gauder de un varietate de interesses creative, e (e) le preservation del memoria e del judicamento. Isto suggere que un del methodos possibile in le evalutation del individuo de etate avantiate e in le definition de su aptitudes mental pote basar se super un concepto de efficacia psychologic e social in general.

3. Le evalutation comprehensive del patiente ambulatori de etate avantiate debe differentiar (a) alterationes physiologic e physic que es relationate al processo de invetulation e determinate per le constitution e (b) patronos social e psychologic de valididate perenne durante le integre vita. Recercas additional con respecto al invetulation va profitar—plus ancora que studios de altere problemas—de un methodologia comprehensive e correlatori in que es combinate le punctos de vista clinic, physiologic, e psychologic. Investigationes de iste genere es ben effectuabile como parte del programma de un clinica geriatric que se occupa de casos requirente un tractamento a longe vista.

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CLINICAL STAFF CONFERENCE

SARCOIDOSIS: CLINICAL STAFF CONFERENCE AT THE NATIONAL INSTITUTES OF HEALTH *

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Dr. John P. Utz: When presenting a conference for our group at the National Institutes of Health, one gets caught on the horns of a dilemma. One horn is to select a subject in which we are very personally and vitally interested. but with the fear if we do so that very few people will be greatly interested in this particular little facet, despite the fact that we could present some rather interesting experimental data. Another horn of the dilemma is to choose something that might be of great interest to many of the Institutes' staff, but on which we may be carrying only a small part of the program, and thereby having to depend upon the graciousness and coöperation of other Institutes to a certain extent. Today, we have chosen to be pinioned on the second horn of this dilemma, and we are very grateful to the many people on the program.

Approximately 30 years before internists in general knew about sarcoidosis, it was recognized by the dermatologists. In fact, the disease bears the eponym of two dermatologists. Dr. Eugene Van Scott, of the National Cancer Institute, will describe the great interest of dermatologists and the very important role they have played in the study of this disease.

DR. EUGENE VAN Scott: The word "sarcoid" is descriptive (sarco-flesh + oid- form) of cutaneous lesions of this disease. Other descriptive terms have been employed to identify various forms of the lesion, such as "lupus pernio," "angio-lupoid," "miliary lupoid," "erythematous sarcoid," etc. The word "sarcoid" has also been used to describe cutaneous lesions of other unrelated diseases, such as erythema induratum (sarcoid nodularis) and a benign type of lymphocytoma (Spiegler-Fendt sarcoid).

Like many diseases that were first recognized in the skin, sarcoidosis is now known to be systemic in nature, with characteristic lesions occurring throughout the body. Although more knowledge of the disease has been gained during the years, sarcoidosis is still a chronic disease, with unknown etiology and without specific treatment.

The histologic resemblance of lesions of sarcoid to those of tuberculosis led physicians in the past to believe that sarcoidosis was caused by a mycobacterium.

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Altered immunologic reactions of patients with the disease, particularly a nonreactivity to tuberculin of many patients, perhaps further strengthened this view. Antituberculosis therapy of the disease, however, has not been significantly beneficial.

A prevalent view today is that sarcoidosis is a granulomatous disease involving the reticuloendothelial system, and that, as in other diseases involving this system, such as the lymphomas, altered immunologic responses are probably consequent to the involvement.

Dr. John P. Utz: Dr. Horace Bernton was a Clinical Associate here from 1953 to 1956, and has since continued his very interesting work in sarcoidosis at the Veterans Administration. Dr. Bernton will discuss the epidemiology of the disease.

Dr. Horace W. Bernton: I should like to describe briefly epidemiologic studies concerning sarcoidosis and the thinking which led investigators in the Veterans Administration to become interested in pine pollen as a possible etiologic factor in sarcoidosis. I shall present data from preliminary studies relevant

to skin reactions to an antigen derived from pine pollen.

To my knowledge, the occurrence of sarcoidosis predominantly in a particular area was first mentioned in 1940 by Dr. H. G. Whitehead, of Johns Hopkins, who alluded to the fact that sarcoidosis occurred in the temperate zones. He felt that the majority of patients with this disease had their origins in rural locations. The first significant statement, however, was made in 1948 by Dr. John C. Ransmeier 2 at a meeting of the National Research Council of Sarcoidosis. He observed that the majority of military personnel afflicted with sarcoidosis had their origins in the southeastern section of the United States. This was followed in 1950 by the first real epidemiologic study of this disease, carried out by Michael, Cole, Beeson and Olson.8 They reviewed 350 cases among veterans of World War II and confirmed Ransmeier's observation. They also noted a high incidence among those of rural background. In 1955 Gentry, Nitowsky and Michael 4 related the occurrence of the disease to the red-vellow podsolic soil of the southeastern United States. In 1956 Cummings and his colleagues,⁵ studying 1,194 cases from 173 Veterans Administration Hospitals, extended the area of high incidence to include all of the eastern United States and eastern Texas. They felt that the concentration of cases correlated best with forest distribution in the United States. Accordingly, a variety of forest products came under study in the Veterans Administration.

Dr. Samuel P. Martin onted that pine pollen was occasionally found in sputum during the pollinating season. This fact led Cummings and Hudgins to institute a study of pine pollen. It was observed that the germinal nucleus of pine pollen—and, indeed, the pollen of all the gymnosperms—was acid-fast when observed with Ziehl-Neelsen stain. It was known that approximately six months earlier Nethercott and Strawbridge had claimed to have found mycolic acid and alpha epsilon diamino pimelic acid, or DAP, in sarcoid tubercles. Since these substances do not normally occur in mammalian tissues and are known to be present in the tubercle bacillus, they reasoned that sarcoido-

sis must be a manifestation of tuberculosis.

Armed with these two facts, Cummings and Hudgins 7 sought to charac-

terize further the lipids in pine pollen, the presence of which was indicated by the acid-fast reaction. With the use of the chemical methods of Anderson, a purified wax fraction was isolated which was quite similar to, but not identical with, mycolic acid and the lipid isolated by Nethercott and Strawbridge. A further search revealed the presence of DAP. Also found in pine pollen were phospho-lipid, chloroform-soluble waxes, firmly bound lipids, and alcoholether soluble lipids. All of these substances are similar to those described in tubercle bacillus. Cummings and Hudgins were also able to produce small local epithelioid granuloma in normal animals injected with pine pollen.

An antigen * was prepared from white pine pollen by extraction with Coca's solution. It was sterilized by tyndallization, and the supernatant was used for injection. This antigen produced delayed-type reactions in guinea pigs previously sensitized with injections of pine pollen. Tuberculin-positive guinea pigs also reacted to the antigen, but animals sensitized to pine pollen did not react

to tuberculin.

Accordingly, several groups of humans were studied, a total of 240 individuals. A 1:1,000, and in some instances 1:500, dilution of the pollen antigen was placed intracutaneously, and reactions were examined one-half hour and 48 hours after injection. One-half centimeter of induration, or larger, constituted the positive reaction, and less than that was considered to be negative. Large wheals with pseudopod formation which were seen at one-half hour were considered to be an acute phase reaction.

One hundred forty-one control patients were studied. Intermediate tuberculin skin tests and pine pollen antigen were placed intracutaneously (0.1 ml.). The total number of positive reactors to tuberculin was 99. Twenty-five per cent gave positive reactions to pine pollen. Among 42 tuberculin-negative in-

dividuals, none reacted to the pine pollen antigen.

Among a group of 62 individuals with active pulmonary tuberculosis, 23 (or 37%) presented positive reactions to pine pollen. These patients were from the Chest Division of the District of Columbia General Hospital. Dr. Sol

Katz and his staff kindly cooperated in this phase of our study.

Among 34 individuals with sarcoidosis, four out of 10 tuberculin-positive cases reacted to pine pollen, and among 24 tuberculin negative patients with sarcoidosis, only one out of 24 (or 4.2%) reacted. Dr. Norman H. Bell, of the National Institute of Allergy and Infectious Diseases, tested several individuals in this particular series.

A patient with culturally proved histoplasmosis who was tuberculin-positive did not react to pine pollen antigen. Two cases of healed histoplasmosis with negative tuberculin reactions were the only instances, other than one case of sarcoidosis, where patients with negative tuberculin responses reacted to the

pine pollen antigen.

The acute-phase reaction frequently arose in 10 to 15 minutes, and occurred in 17% of individuals from all four age groups. The acute phase reactors were not clustered in any particular group. This finding was of interest to us because acute-phase reactions to antigens made from pine pollen are relatively unknown. Some of the reactions may have been nonspecific, because concen-

^{*}Mr. Paul Hudgins, Tuberculosis Research Laboratory, Veterans Administration Hospital, Washington, D. C., prepared the antigen and performed the early guinea pig tests.

tration of antigen was greater than that commonly used by allergists in clinical testing. To our knowledge, only one case of clinical allergy due to pine pollen is reported in the literature.⁹ It is our belief that the antigens as made by allergists contained very little Kjeldahl nitrogen, because pine pollen is very resistant to extraction unless it is first broken up with a ball mill. It resists acid hydrolysis for 24 hours, and is an amazingly strong cell.

The data presented suggest that pine pollen sensitivity of the delayed type is somewhat related to the tuberculin status of the individual tested. Fifty-two of 172 tuberculin-positive subjects gave delayed-type reactions to pine pollen antigen, and only three out of 68 tuberculin-negative individuals reacted to the antigen. Of these, two had healed histoplasmosis and one had sarcoidosis.

The incidence of positive reactors to pine pollen is higher in the group with active pulmonary tuberculosis. This group has a higher degree of sensitivity to tuberculin than patients without active clinical disease. It may be that, with further purification and concentration of the antigen, a greater number of positive pine pollen tests will be noted in tuberculin-positive subjects.

These studies are directed rather obliquely toward sarcoidosis, since these patients are notoriously anergic to antigens placed in the skin. Perhaps we are learning about pine pollen sensitivity as it relates to tuberculin sensitivity, and are not directly increasing our knowledge of the etiologic agents in sarcoidosis.

In other laboratories within the Veterans Administration, however, more direct approaches are being made. Specifically, attempts are being made to demonstrate pine pollen and its derivatives in sarcoid granuloma, and also to demonstrate specific antibodies against pine pollen in the sera of patients with sarcoidosis.

In summary, it is evident that the basic pathologic changes in sarcoidosis are similar in many respects to those seen in noncaseating tuberculosis. There is a high incidence of sarcoidosis in areas forested primarily by pine trees, and this epidemiologic clue is serving as a basis for laboratory and clinical studies. Also, there appear to be chemical and immunologic similarities between pine pollen and the tubercle bacillus.

Dr. John P. Utz: Those of us caring for sarcoid patients in the Clinical Center have had to depend to a great extent on consultations with the Pathology Department in regard to the final diagnosis for these patients. Besides being a syndrome of symptoms and signs, the disease also has characteristic pathologic features to which reference has been made.

We are pleased to have Dr. John H. Edgcomb discuss the pathologic features of sarcoid and the Kveim reaction.

Dr. John H. Edgcomb: I shall discuss briefly the pathologic findings in patients with sarcoidosis and the morphology of the Nickerson-Kveim test.

Sarcoidosis is a disease during which noncaseous granulomas may occur in almost any organ of the body. The diagnosis depends as much on the clinical as on the pathologic characteristics of the disease. Clinical criteria for diagnosis include hypercalcemia, hyperglobulinemia, and anergy to tuberculin. Pathologic criteria include the presence of "hard," or noncaseous, granulomas, and a failure to demonstrate organisms or chemical substances which could have caused the

granulomas. A pathologic diagnosis of sarcoidosis is reached by a process of exclusion. Lesions are frequently interpreted as "granulomatous inflammation, consistent with sarcoidosis." ¹⁰

No one has demonstrated a primary complex in sarcoidosis comparable to the Ghon complex of tuberculosis. Pulmonary infiltrates seen early in the course of the disease are almost invariably bilateral. In biopsy material the granulomas are characteristically in the same stage of development (figure 1).

Sarcoid granulomas consist of epithelioid cells, multinucleated giant cells, various inflammatory cells, and concentric and interlacing fibers which are



Fig. 1. Sarcoid granulomas, skin. Hematoxylin-eosin. 50 x.

argentophilic or stain as collagen (figure 2). Aging of sarcoid granulomas is associated with progressive fibrosis and hyalinization.

Calcium salts sometimes deposit in sarcoid granulomas. The deposits may occur as irregular precipitates on fibers, or as small, laminated concretions, the Schaumann bodies (figure 3). In some giant cells, stellate, eosinophilic "asteroid bodies" may be seen in the cytoplasm (figure 4). Similar structures have been described in myeloma cells.

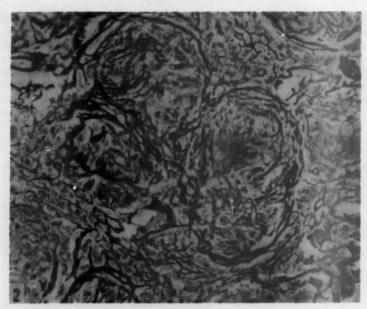


Fig. 2. Argentophil reticular fibers at periphery of sarcoid granulomas, lymph node. Wilder reticulin stain. $165 \times .$

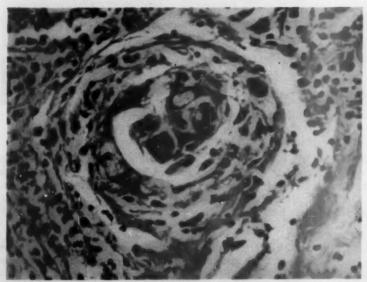


Fig. 3. Schaumann bodies, microscopic concretions containing calcium, seen in sarcoid granuloma, lymph node. Hematoxylin-eosin. $250 \times .$

Williams and Nickerson ¹¹ in 1935 and Kveim ¹² in 1941 described a diagnostic test for sarcoidosis. A crude suspension of ground tissue containing sarcoid granulomas is injected subcutaneously, and the site of injection is biopsied from three to six weeks after the injection. The presence of a non-caseating granuloma is considered by some to be diagnostic of sarcoidosis (figure 5). Others consider the test to be of no value. ¹³ There is no uniform central source of Kveim "antigen," and the amount of extraneous material capable of inciting foreign-body granulomas varies from preparation to preparation. Foreign-body granulomas can be distinguished from sarcoid granulomas. Their presence does not constitute a positive Nickerson-Kveim test. ¹⁴

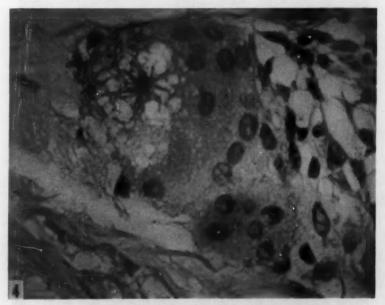


Fig. 4. Asteroid body, giant cell, sarcoid granuloma, lymph node. Hematoxylin-eosin. 700×.

Dr. John P. Utz: Of the 30 or more patients we have seen in the Clinical Center during the last four or five years, we have rarely encountered arthritic complaints or signs of arthritis. It was extremely interesting, therefore, to hear that Dr. Joseph Bunim and others at the National Institute of Arthritis and Metabolic Diseases had been studying a group of sarcoid patients with arthritic lesions. Dr. Bunim will tell us about them.

Dr. Joseph J. Bunim: Until 1952, joint involvement in sarcoidosis received little or no attention in the medical literature, or even in extensive reviews or monographs on sarcoidosis. Since 1952, however, three papers have reported the incidence of arthritis to be 25, 10 and 22%, respectively. We suspect that sarcoid arthritis may have been mistaken for rheumatoid arthritis or rheumatic

fever, since they have some clinical features in common, although it is conceivable that these diseases may coexist.

During the last two years, Dr. Leon Sokoloff and our group of clinical investigators at the National Institute of Arthritis and Metabolic Diseases have been engaged in a preplanned study of the clinical, laboratory and pathologic features of joint disease in sarcoidosis, and thus far have studied five cases.

I should add that the study is still in progress, and we are very much interested in augmenting our series. I should like to summarize our findings to date.

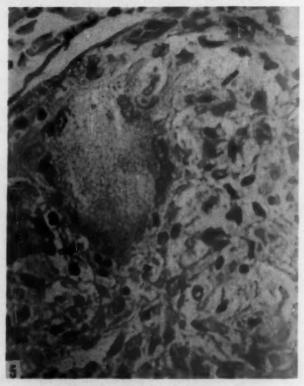


Fig. 5. Granulomatous inflammation, site of positive Kveim-Nickerson test, skin, arm. Hematoxylin-eosin. 335 ×.

Table 1 is a tabulation of the joint findings. There are five patients, all Negroes—four females and one male. Incidentally, they all came from the southeastern area of this country. The age of onset of arthritis varied from nine to 33 years. As you can see, this condition existed in the younger age group. The onset of arthritis occurred at the very beginning of sarcoidosis in three of the five patients, and in the other two cases it developed two years after onset of the disease.

Duration of the arthritis varied from several days, weeks or months, to

four and one-half years in the most severe case. The joints involved were small and large, but they were all peripheral, and in only one instance were the symptoms related to the neck as well as to the peripheral joints.

The objective signs were those of inflammation; in one patient there were heat and redness in addition to tenderness and swelling. Of the five patients, four showed no evidence of permanent joint damage; only one had permanent damage, and we will discuss this case later. Only one of the five patients had fever. In the others, the temperature was normal, which point distinguished it from rheumatic fever. The response to aspirin was good in two patients and moderate in two others, which may cause this condition to be confused with rheumatic fever and rheumatoid arthritis.

TABLE 1
Summary of Joint Findings

| Case | 1 | 2 | 3 | 3 4 | | |
|---------------------|---------------------|---------------------|------------------------------|---------------------------------|---------------------------------------|--|
| Race, sex | NM | NF | NF | NF | NF . | |
| Age at onset | 28 | 33 | 22 | 31 | 9 | |
| Onset of arthritis | 2 yrs. | 1st wk. | 1st symp. | 1st symp. | 2 yrs. | |
| Duration | 41 yrs. | 4 wks. | 2 yrs. | 3-4 mos. 7-8 mos. 2½ yrs. | 3-10 days | |
| Joints affected | F, T, E | K, S, E, W, A, F | K, F, W, E, A | K, A, S, W, E, neck | F, T, W | |
| Objective changes | Tender, swelling | Tender | Tender, swelling, heat | Tender, swelling | Tender, swelling, heat, redness | |
| Joint destruction | Severe, fingers | None | None | None | None | |
| Fever | None | 101.8 | None | None | None | |
| Response to aspirin | - | Good | Mod. | Mod. | Good | |

Table 2 documents evidence that the patients had systemic sarcoidosis, skin manifestations, uveitis, and both peripheral and hilar adenopathy. Four of five patients had pulmonary infiltration. One patient had parotitis and three had sarcoid bone disease, which is to be distinguished from sarcoid joint disease. In two of the three patients who had sarcoid bone disease there was no contiguity between the bone and the joint involved. Some patients had hepatomegaly, and one had splenomegaly. In every case, biopsy of one or several tissues was positive. For example, in one patient synovial biopsy and skin biopsy were characteristic of sarcoid granulomata; the muscle, however, was negative. In another patient a positive biopsy was obtained in the synovium, lymph node, muscle and liver; in a third patient, in the synovium and skin; in a fourth patient, in the synovium and lymph node; and in a fifth patient the skin was

TABLE 2
Manifestations of Sarcoidosis

| Case | 1 | 2 | 3 | 4 | 5 |
|------------------|--------------|---------------------------------|--------------|------------|---------------------|
| Skin | Sarcoid | Erythema nodosum | Sarcoid | None | Leg ulcer |
| Eye | None | Uveitis | None | None | Uveitis |
| Adenopathy | SI. | + | + | + | + |
| Hilar adenopathy | Min. | + | + | + | ± |
| Pulmonary | + | + | None | + | + |
| Parotitis | None | + | None | None | None |
| Bone | Dactylitis | Feet | None | None | Dactylitis |
| Hepatomegaly | None | 3F | 1F | None | 2F |
| Splenomegaly | None | None | None | None | 2F |
| Biopsy positive | Synov., skin | Synov., LN, muscle, liver | Synov., skin | Synov., LN | Skin |
| Biopsy negative | Muscle | None | LN | Muscle | Non-spec. synov. |

positive and the synovia showed synovitis but not a characteristic lesion of sarroidosis.

Table 3 is a tabulation of the laboratory findings. It is interesting and useful to know that the hemagglutination reaction or the bentonite flocculation test, which is positive in 85% of definite cases of rheumatoid arthritis, is negative in every one of these patients. So it is a useful serologic, differential diagnostic aid. C-reactive protein was positive in three of the five cases; sedimentation

TABLE 3
Summary of Laboratory Findings

| Case | 1 | 2 | 3 | 4 | S |
|-----------------------|-------------|---------|---------|---------|---------|
| SCA or BFT | Neg. | Neg. | Neg. | Neg. | Neg. |
| CRP | | 4+ | 2+ | - | 4+ |
| ESR | 15 | 83-101 | 76 | 85 | 100 |
| WBC | 4,800-6,400 | 14,000 | 7,100 | 6,000 | 4,200 |
| Eosinophils | 4-9 | 2 | 6 | . 3 | 2, 3, 5 |
| Synovial fluid WBC | | - | 1,200 | 1,025 | |
| Mucin clot | - | - | Normal | Normal | - |
| A/G | 3.4/3 | 2.8/4.6 | 3.4/4.4 | 3.8/4.5 | 2.4/5.5 |

TABLE 4
Summary of Microbiological Findings

| Case | 1 | -2 | 3 | 4 | 5 |
|--------------------------------|--------------|--------------|--------------|--------------|--------------|
| Tuberculin | _ | PPD 2:4+ | PPD 2:3+ | Neg. | Neg |
| Histoplasmin | _ | Neg. | Neg. | Pos. | Neg |
| Coccidioidin | - | Neg. | Neg. | ****** | Neg. |
| Sputum AFB | Neg. | Neg. × 20 | _ | Neg. | _ |
| Gastric AFB | | Neg. | - | Neg. | Neg. |
| Biopsy GP | _ | Neg. | Neg. | Neg. | _ |
| Biopsy culture AFB Fungi | Neg. Neg. | Neg. Neg. | Neg. | Neg. Neg. | Neg. Neg. |
| Biopsy stain AFB Fungi | Neg. Neg. | Neg. Neg. | Neg. Neg. | Neg. Neg. | Neg. |



Fig. 6. In the roentgenogram, destructive changes are present in the distal phalanges, the distal interphalangeal joints and immediately adjacent portions of the heads of the middle phalanges. Several proximal interphalangeal joints are affected similarly and are surrounded by increased soft-tissue shadows. (Reprinted by permission of New England Journal of Medicine.)

rate was elevated in every case; these findings might cause confusion with rheumatoid arthritis. The white blood count was elevated in one case and normal in all the others, which again is common in rheumatoid arthritis cases. Eosinophilia was present in a few of the patients. Synovial fluid showed a normal mucin clot, which distinguishes it from rheumatoid arthritis, in which almost invariably the mucin clot is abnormal. The A/G ratio was inverted in all five cases.

Table 4 provides additional laboratory data to document the fact that these patients did not have tuberculosis (although in two of the three the tuberculin test was positive): the histoplasmin test was negative; the coccidioidin test was negative; the sputum test for acid-fast bacilli was negative. In every case, gastric secretions tested for acid-fast bacilli were negative. The biopsy tissues previously mentioned were inoculated into guinea pigs with negative results, and when cultured for acid-fast bacilli and fungi, in every case were found to be negative. Special stains of these biopsy tissues were negative for acid-fast bacilli and fungi. Thus, the diagnosis in these cases is clear-cut; tuberculosis or fungal infections have been ruled out.

Figure 6 is an x-ray picture of a patient's hands which showed severe bone destruction. This patient is interesting because he also had most conspicuous articular involvement of the left elbow, an x-ray of which, however, showed absolutely no bone destruction. Here in the terminal phalanges, where there is bone destruction, there were very few articular symptoms. One can see destruction at the distal interphalangeal joint of almost every finger, and the proximal interphalangeal joint of the small finger as well. The metacarpophalangeal joints are clear, which is most unusual in rheumatoid arthritis. Also, the wrists are normal, and usually they are affected in rheumatoid arthritis.

We believe there are two routes of dissemination to the joint. By hematogenous dissemination, the invading agent either may reach the synovial lining directly, causing a granulomatous synovitis, or may invade bone alternatively. In the latter case the granuloma which follows may then spread by direct extension through the articular cortex and cartilage into the joint. In the patient under consideration (figure 6) the first route was followed to the elbow joint (synovitis without bone destruction), and the second to all the distal interphalangeal joints (with severe bone destruction).

DR. JOHN P. UTZ: Just as it was fascinating to hear about arthritis in sarcoidosis, so is it of great interest to follow quite closely the work of the next essayist who is investigating the ferrokinetics and erythrokinetics of a group of patients with sarcoidosis, in whom as a general rule we have not seen anemia. Dr. Norman H. Bell will describe these studies.

Dr. Norman H. Bell: Anemia of any type has been infrequently associated with sarcoidosis. We have recently had the opportunity of studying 13 patients having sarcoidosis, using Fe⁵⁰ and Cr⁵¹ to measure the rate of iron turnover, blood volume and red cell survival. None of the patients was found to have a hemolytic anemia. Hypoferremia in the absence of hemolysis was found to occur frequently, and was in some instances associated with a rapid plasma iron disappearance. In several of the more chronically ill patients having normal hemograms, a reduction of both total blood volume and red cell mass was found.

These findings are clearly the result of diminished erythrocyte production, rather than of increased destruction, and are similar to those obtained by Berlin et al. ¹⁶ and Hollingsworth and Hollingsworth ¹⁷ in patients with pulmonary tuberculosis.

Dr. John P. Utz: How many sarcoid patients go to the doctor first because of trouble with their vision? I do not know the answer, but investigators conducting a uveitis study have seen a number of patients with sarcoidosis. Dr. Herbert E. Kaufman has agreed to describe some of the ocular findings in sarcoidosis.

Dr. Herbert E. Kaufman: Although the pathologic physiology of ocular sarcoidosis appears to be similar to that of systemic sarcoidosis, the eye is so delicate and specialized that inflammation of a degree which might be insignificant elsewhere in the body may cause blindness. Ocular involvement occurs in nearly 50% of patients with sarcoidosis. Aside from the lymph nodes, the eyes and ocular adnexae are the most frequently involved organs. It therefore seems worth while to review some of the most frequent ocular manifestations, and to discuss the possible prevention of serious complications by early recognition and therapy.

Iridocyclitis is the most frequent and important lesion of ocular sarcoid. Pain, redness and photophobia may occur, but usually the inflammatory symptoms are few, and the unremitting course may lead to loss of vision without pain. Between 25 and 50% of cases with this type of anterior uveitis show pink, highly vascularized nodules on biomicroscopic examination of the iris. In other cases, however, the chronic iridocyclitis is not morphologically distinctive. Anterior uveitis in patients with sarcoidosis can be associated with swelling of the parotid and submaxillary glands, and in about one third of these cases with parotid involvement, facial palsy (Heerfordt's disease) is seen. On the other hand, glandular involvement (Mikulicz's disease) may occur in the absence of eye changes.

Recognition by the internist that a relatively asymptomatic iridocyclitis is common in this disease is of importance in that:

1. If left untreated, the inflammation may produce complicated cataracts, secondary glaucoma and, eventually, loss of function of the eye. The progress of the disease can sometimes be controlled with topical and systemic corticosteroids. Thus, systemic corticosteroid therapy may be indicated in the absence of severe systemic involvement.

2. The iritis of sarcoidosis tends to produce early adhesions between the iris and lens which may result in secondary glaucoma. Although this condition can sometimes be relieved surgically by peripheral iridectomy, the effect of operation in the presence of the inflammatory process jeopardizes the outcome. Recognition of the iridocyclitis and prevention of adhesions by dilating the pupil may forestall this serious complication.

3. The combination of inflammation and disordered calcium metabolism favors early deposition of calcium beneath the epithelium of the cornea in the form of a band keratopathy. The proper use of chelating agents can remove these calcium deposits before permanent damage to the cornea results.

4. Corticosteroid therapy, in itself, may, in a small percentage of patients, precipitate secondary glaucoma. In a predisposed inflamed eye the possibility

of inducing iatrogenic glaucoma with subsequent loss of vision must be kept in mind. Pain or blurring of vision must serve as a warning sign.

Although lids, conjunctivae, sclera, episclera and orbital structures may be the site of sarcoid nodules, and the retina and choroid are occasionally involved in the disease, I have attempted to limit my remarks to the most common manifestations and complications that may be preventable by early diagnosis.

Dr. John P. Utz: I am very sorry that Dr. Shy is not here today to discuss some of the National Institute of Neurological Diseases and Blindness electromyographic studies on sarcoid patients.

This would have provided one additional, though perhaps unnecessary, piece of evidence that sarcoidosis is a disease of interest in many fields of medicine.

SUMMARIO IN INTERLINGUA

In 1899 Boeck creava primo le termino "sarcoide" e distingueva inter iste morbo cutanee e alteres. Subsequentemente nove information esseva colligite relative a sarcoidosis, non solmente ab le puncto de vista dermatologic sed etiam in altere respectos. Quanto al epidemiologia, il existe reportos de un augmento del incidentia de sarcoidosis in le sud-est del Statos Unite, e in certe studios usque a 40 pro cento del patientes sarcoide reageva a polline del pinos que es commun in ille areas. Iste polline es chimica- e immunologicamente simile a certe lipidos trovate in le bacillo tubercular. Le lesiones sarcoide ha essite characterisate microscopicamente, e le presentia de duo curiose entitates ha essite constatate in ille lesiones: le corpore de Schaumann e le corpores asteroide in cellulas gigante. Currentemente le test de Nickerson-Kveim se trova sub evalutation in un studio cooperative.

Depost 1952, tres publicationes ha reportate un incidentia de arthritis in sarcoidosis amontante a 25, 10, e 2 pro cento. Cinque patientes con sarcoidosis e arthritis al Centro Clinic esseva studiate intensemente. Iste forma de arthritis esseva cautemente distinguite ab arthritis rheumatoide e ab arthritis tuberculotic e fungal. Certes inter iste patientes e certe alteres esseva studiate con respecto a lor hypercalciemia e hypercalciuria, e il pare que iste defecto es possibilemente le resultato del absorption de un inusualmente grande quantitate de calcium ab le dieta. Certes inter iste patientes beneficiava ab un therapia con steroides.

Ben que, a generalmente parlar, anemia ha non essite considerate como un manifestation de sarcoidosis, studios per le autores ha monstrate que un considerabile procentage de patientes sarcoide se distingue per un basse contento seral de ferro, un rapide disparition de ferro ab le plasma, un reducite metabolismo de ferro in plasma e erythrocytos, e un reduction tanto in le volumine erythrocytic como etiam in le volumine del sanguine, e omne isto in despecto de un hematogramma normal. In plure series de patientes sarcoide, usque a 50 pro cento habeva complicationes ocular, con iridocyclitis como le plus commun. Calaractas, glaucoma secundari, e—in le curso del tempore—cecitate es possibile disveloppamentos secundari. Es sublineate le desiderato de un precoce diagnose del affection ocular, a un tempore quando su progresso es ancora prevenibile per medio de un therapia corticosteroide.

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CASE REPORTS

THE SYMPTOMS OF HYPERCALCEMIA ASSOCIATED WITH SARCOIDOSIS MASQUERADING AS PEPTIC ULCER*

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HYPERCALCEMIA occurs in sarcoidosis with sufficient frequency to merit special consideration.¹ Likewise, the gastrointestinal symptom complex of hypercalcemia has received attention in recent years.².⁵ Gastrointestinal symptoms as a primary presenting symptom of hypercalcemia of sarcoidosis have been mentioned only infrequently in many of the articles reviewed. Failure to recognize this important diagnostic clue may lead to erroneous interpretation, causing

exaggeration of symptoms, as noted in the patient here reported.

Hypercalcemia, when discovered, usually leads the clinician first to consider primary hyperparathyroidism, hypervitaminosis D, metastatic malignancy and multiple myeloma.4 Less common causes include the "milk alkali syndrome of Burnett," Paget's disease, osteoporosis (rarely), Hodgkin's disease, hyperthyroidism,5 and malignancy per se (i.e., lung, kidney, uterus and lymphosarcoma), even without evidence of bone involvement.6 Sarcoidosis should be included in this latter group of diseases, since it produces hypercalcemia in about 20% of cases. The pathologic physiology producing hypercalcemia in these various entities differs widely, but appears to be related to the increased absorption of calcium from the gastrointestinal tract in sarcoidosis and hypervitaminosis D. The fact that patients with sarcoid develop hypercalcemia on an intake of from 30,000 to 140,000 units of vitamin D per day, while control patients rarely demonstrate this on a dosage under 200,000 units a day for months or years, is strong evidence for this mechanism. Henneman et al.¹ believe this suggests an endogenous vitamin D intoxication. Hypercalcemia and hyperproteinemia may occur independently of each other and at different stages of sarcoidosis. Hence, the binding of large amounts of calcium by the abnormal serum globulins is not the primary mechanism producing hypercalcemia. Bone erosion and absorption were once thought to be a factor in the production of hypercalcemia. Sarcoid patients with hypercalcemia and even radiologically demonstrable nephrocalcinosis, however, do not necessarily show evidence of either bone destruction or demineralization.7

Complaints arising from the gastrointestinal system often occur in patients with hypercalcemia of hyperparathyroidism. The symptoms are chiefly those of anorexia, nausea, bloating, and epigastric burning and pain, as well as vomiting. Hypercalcemia from other causes may produce a similar symptom complex. St. Goar a reported gastrointestinal complaints in 16 of 45 patients with

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hyperparathyroidism, while Snapper [®] described the "digestive syndrome" but believed it to be an infrequent occurrence. The mechanism of this symptom complex is not clear, but it is probably produced in several ways. The increased calcium ion concentration impedes the transmission of afferent stimuli and diminishes efferent discharges within sympathetic ganglia in the presence of a constant amount of acetylcholine. In addition, the reduced neuromuscular excitability produced by hypercalcemia brings about decreased gastrointestinal muscle tone. The relative atony of the gut is believed to be the cause of the majority of symptoms, although nausea and vomiting are occasionally seen immediately after the injection of calcium gluconate intravenously. The mechanism of this rapidly appearing symptom is likewise poorly understood.

An equally baffling observation has been the questionable association of peptic ulcer and hyperparathyroidism. St. Goar ⁸ reported an incidence of 8.8% in his series of 45 cases. A review of patients with hyperparathyroidism at Massachusetts General Hospital showed an incidence of ulcer in 12 of 137 patients. This would appear to be clinically significant, although investigators in this field are reluctant to stress this point. The been observed that parathyroidectomy in these patients often cures the complicating peptic ulcer as well as the hyperparathyroidism. There does not appear to be an increased incidence of peptic ulcer in conditions known to produce hypercalcemia, except in hyperparathyroidism. Less common is the finding of acute pancreatitis in patients with hyperparathyroidism. Cope ¹⁰ reported a series of patients in whom pancreatitis antedated the discovery of clinical hyperparathyroidism.

It is therefore apparent that the gastrointestinal symptoms of sarcoidosis cannot be ascribed to organic involvement of this system until hypercalcemia is ruled out. Nevertheless, infiltration of the stomach with granulomatous lesions and, more frequently, involvement of the liver occur in this disease. Postmortem studies have demonstrated that there is an incidence of liver involvement of 60 to 75% in sarcoidosis. Hepatic sarcoidosis can be so extensive as to produce portal hypertension, with subsequent bleeding esophageal varices requiring porto-caval anastomosis. Massive gastrointestinal hemorrhage due to hypersplenism and thrombocytopenia, gastric ulcerations from sarcoid infiltration and gastric ulcer the per se have all been observed in sarcoidosis. No consistent hemorrhagic diathesis appears to be associated with hepatic sarcoid disease, and no incidence of hypoprothrombinemia has been documented.

The following case report describes a patient with sarcoidosis and hypercalcemia who developed gastrointestinal symptoms which masqueraded as peptic ulcer.

CASE REPORT

History: A 35 year old white male presented himself on January 9, 1957, with complaints of nausea, weakness, mild epigastric distress and abdominal fullness. His occupation was that of a dispenser of "Frozen Milk." His symptoms had occurred intermittently since 1952, at which time he was admitted to a local hospital because of tarry stools. Subsequent x-ray examinations showed this to be due to an active duodenal ulcer, and he was given a diet, antispasmodics and iron. He was asymptomatic from 1952 until January 12, 1954, when he was first seen by this observer because of abdominal gas, distention and a gnawing sensation beginning one hour

after meals. This distress was relieved by milk, food and alkali. At that time, physical examination, including the abdomen, was negative. Antispasmodics and antacid measures, together with diet restriction, were effective in therapy. Gastrointestinal x-rays at this time were refused. A similar episode was noted on July 7, 1955, when a mild bout of abdominal distress, gas and bloating sensations occurred, without significant findings on physical examination. The patient reported no distress in the interim, but readily admitted to much emotional conflict, i.e., indecisions as to work, and worries about his children and home responsibilities, mortgages and financial strains. There had been no vomiting, change in bowel habit, weight change, melena or food intolerance.

Past history was uneventful except for recurrent epistaxis with upper respiratory infections. The patient had sustained a fractured right femur in 1936 due to trauma. He denied the use of tobacco in any form, alcohol, or excessive coffee or tea intake. His father had suffered repeatedly with peptic ulcers and died of unknown causes at the age of 52.

TABLE 1

| Procedure | 2/16/57 | 2/18/57 | 3/15/57 | 4/22/57 | 12/6/57 | 3/26/58 |
|---|---------|-------------------|---------|---------|--------------------|-------------------|
| Serum calcium (mg./100 ml.) | 14.5 | 15 | 11.64 | 14.1 | 9.6 | 8.84 |
| Serum phosphorus (mg./100 ml.) | | 3.7 | 2.53 | | | 2.1 |
| Total serum proteins (gm. per 100 ml.) Albumin Globulin | | 7.0 4.3 2.7 | | | 7.5 4.5 2.65 | 7.1 4.5 2.6 |
| Serum alkaline phosphatase (King-Armstrong U.) | | 9.5 | | | | 9 |
| BUN (mg./100 ml.) | | 12.5 | | | | 8.5 |

Physical Examination: Height, 5 feet 10 inches; weight, 175 pounds; temperature, 98° F.; blood pressure, 138/75 mm. of Hg. The patient was a blond, muscular white male with a rather worried facies. There were bilateral pterygii, but no abnormalities were seen in the iris or lens of the eyes. The funduscopic examination was normal. There was no superficial adenopathy. There were no abnormalities in the lungs or heart. A smooth, nontender liver edge was palpable 2 cm. below the right costal margin. The spleen was not palpated, nor was enlargement demonstrable by percussion. No abdominal tenderness, spasm or percussion tenderness was present over the upper abdomen. No bone or spine tenderness could be elicited. Neurologic examination showed no abnormality.

Laboratory (table 1): Urinalysis, negative for albumin, sugar and acetone, with no microscopic abnormalities, specific gravity, 1.015. Hemoglobin, 14 gm.; hematocrit, 46%; white blood cell count, 8,550, with a normal differential. Stools were repeatedly negative for blood by the benzidine dihydrochloride test. The erythrocyte sedimentation rate was 15 mm. in one hour (Wintrobe method). Serum bilirubin direct, slight trace; indirect, 0.7 mg. An upper gastrointestinal x-ray showed an old duodenal ulcer deformity, plus what appeared to be a somewhat oblong crater along the posterior wall of the duodenum. Gastric analysis showed 15° free hydrochloric acid, and total acid of 35°, with negative occult blood and lactic acid studies. Bromsulfalein test, Hanger's test, prothrombin time, serum alkaline phosphatase and

total serum proteins were normal. Histoplasmin, coccidioidin and first and second strength purified protein derivative (PPD) skin tests were negative.

Clinical Course: An ulcer diet, antacids (Alkets) and belladonna were administered because of the supposed ulcer crater and the history of previous melena during an acute ulcer episode. When next seen, two weeks later, the patient complained of even more gas and epigastric fullness, together with aching in his jaws and injection of the sclera. He failed to receive relief with milk, antacids or food. A second upper gastrointestinal x-ray was reported as showing hypertrophic rugae, plus the previously noted duodenal deformity and an area thought to represent a small crater (or old scar). Because of the lack of response to an ulcer regimen the patient was hospitalized on February 5, 1957. He was put at bed-rest and given sedation, an ulcer diet, Pro-banthine, 30 mg. every six hours, and Gelusil every two hours, with no demonstrable relief of symptoms after a full two-week trial. A final upper gastrointestinal x-ray study was then attempted in an effort to shed some additional light on his symptoms. It was at this time that hilar adenopathy was first reported by the radiologist as an incidental finding. Previous chest fluoroscopies, done at the time of the upper gastrointestinal series, had been reported as normal. The hilar adenopathy was confirmed by chest x-rays (figure 1).

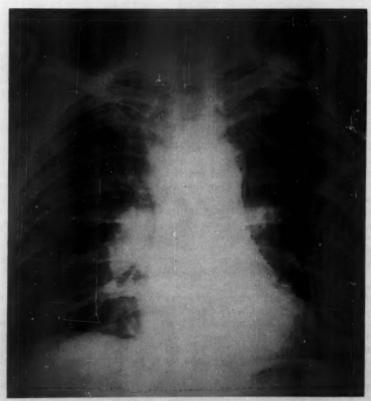


Fig. 1. Chest x-ray, demonstrating bilateral hilar adenopathy.

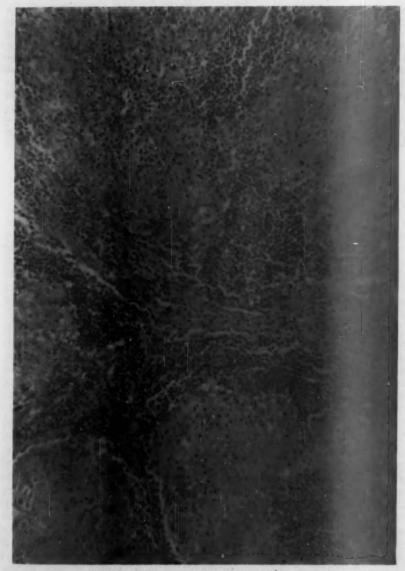


Fig. 2. Scalene node biopsy, showing the typical granulomatous lesions of sarcoidosis.

A diagnosis of sarcoidosis was confirmed by a right scalene node biopsy (figure 2). A liver needle biopsy was suggested but refused. Subsequent determinations of serum calcium (table 1) led to the immediate discontinuance of the antacids, anticholinergic drugs, and additional milk, which was followed by relief of symptoms

within 72 hours. It is interesting that with the discontinuance of an ulcer regimen and substitution of a low calcium diet the patient's abdominal symptoms were completely relieved and the serum calcium and phosphorus dropped to within normal limits in three weeks (table 1). This occurred without any additional treatment. An even more interesting incident was the return of symptoms three months later (May, 1957), again associated with elevation of the serum calcium. When confronted with this evidence and questioned closely relative to his dietary intake, the patient readily admitted to the discontinuance of the low calcium diet and increased intake of milk products (Frozen Ice Milk), one to two pints a day. When last seen (March, 1958), he had been asymptomatic for nine months, and no abnormality was noted in the serum calcium, phosphorus, total serum proteins, serum alkaline phosphatase or blood urea nitrogen. Sulkowitch's test was 1 plus. Follow-up chest x-rays showed a slight decrease in the hilar adenopathy on the right.

DISCUSSION

Many pitfalls were encountered and much unnecessary gastrointestinal distress was endured before the exact nature of this patient's symptoms was discovered. One might conjecture that his symptomatology, dating from 1954, was not due to an active ulcer, inasmuch as no abdominal tenderness was present and no occult blood was ever discovered in spite of frequent stool examinations. The fact that an acute ulcer crater was visualized and melena observed in 1952 led to the conviction that all subsequent abdominal complaints were due to the same cause. The failure to relieve symptoms with an intensive ulcer regimen under hospital control was an indication to consider other diagnoses.

It is possible that the milk-alkali syndrome was present here, but it is doubtful that there was an excessive ingestion of soluble alkali, nor were the antacids and milk products given over a protracted period of time. Furthermore, the lack of vomiting and the absence of any renal impairment make this diagnosis unlikely, though still a consideration. The rapid disappearance of symptoms, the return of the laboratory tests to normal values and the absence of alkalosis

all tend to nullify this diagnosis.

Much attention and effort have recently been directed toward steroid therapy in sarcoidosis. The beneficial effect of cortisone as a therapeutic agent against hypercalcemia, hypercalciuria, nephrocalcinosis and renal insufficiency is suggested by Gleckler.15 Intensive cortisone therapy causes an increase in fecal and urinary excretion of calcium. Soffer 16 suggests that cortisone produces increased excretion and reduced absorption of calcium from the digestive tract. It has been noted that since vitamin D and cortisone possess similar structural formulae, there may be a direct antagonism between these substances in their action on calcium metabolism.17 Cortisone therapy has a dramatic and prompt effect on serum calcium levels as well as on the clinical course in critically ill patients with hypervitaminosis D.18, 19 It is a common experience, however, to observe alleviation of symptoms in sarcoidosis under steroid therapy without demonstrable change in size of glands, skin lesions or pulmonary function. 30, 21 Steroids were felt to be definitely contraindicated in this patient, since there was a previous diagnosis of bleeding duodenal ulcer. Furthermore, without evidence of renal impairment, simple reduction of calcium intake will often reduce the hypercalcemia, as it did in this patient.

SUMMARY

Hypercalcemia with marked gastrointestinal symptomatology is described in a patient with sarcoidosis who was receiving treatment for peptic ulcer. A previously demonstrated bleeding duodenal ulcer led to the institution of ulcer therapy, followed by exaggeration of symptoms. These gastrointestinal symptoms were promptly alleviated by a reduction in dietary intake of calcium. The interesting interrelationship of sarcoidosis, hypercalcemia, peptic ulcer and the milk-alkali syndrome is discussed. The important signals of nausea, abdominal fullness and vague epigastric distress should not be overlooked as a presenting complaint of hypercalcemia.

SUMMARIO IN INTERLINGUA

Hypercalciemia con marcate symptomas gastrointestinal pote occurrer in patientes con sarcoidosis qui es tractate pro ulcere peptic. Es opinate que iste augmento del calcium in le sero es le resultato de un augmento del absorption de calcium ab le vias tomas de anorexia, nausea, un sensation de inflation e plenitude epigastric, e mesmo hypervitaminosis D, post multo plus basse dosages de vitamina D que normal subjectos de controlo, e on ha suggerite que isto representa un intoxication per vitamina D endogene. Hypercalciemia ab non importa qual causa produce usualmente symptomas de anorexia, nausea, un sensation de inflation e plenitude epigastric, a mesmo dolor e vomito. Le mechanismo del symptomas abdominal non es clar, sed il pare plausibile supponer que il se tracta de un augmento del tono in le musculos gastrointestinal. Le symptomas gastrointestinal in sarcoidosis es ascribite le plus frequentemente a un affection del hepate o al infiltration de lesiones granulomatose in le pariete intestinal. Isto pote esser si extense que illo produce hypertension portal, hypersplenismo, o hemorrhagia gastrointestinal ab le ulceration del intestinos. Il non pare occurrer un augmentate incidentia de ulcere peptic in conditiones que cognoscitemente produce hypercalciemia in comparation con le incidentia de ulcere peptic que es incontrate in hyperparathyroidismo.

Es reportate le caso de un masculo de racia blanc de 35 annos de etate con un historia de sanguinante ulcere duodenal. 'Le symptomas initial de nausea, disconforto e plenitude epigastric esseva interpretate como attribuibile a un recurrentia de ulcere. Tamen, un adequate conducta therapeutic pro ulcere, con augmento del ingestion de lacte, resultava in un acerbation del symptomas. Post plure examines a radios X que non produceva probas conclusive de ulceration real, adenopathia hilar esseva notate. Subsequentemente un biopsia de nodo scalen esseva effectuate, e isto demonstrava le presentia de sarcoidosis. Initialmente le calcium del sero del patiente amontava a 14,5 g. Le symptomas del patiente esseva alleviate promptemente con le discontinuation del regime pro ulcere. Concomitantemente le calcium del sero regredeva. Le mesme symptomas retornava duo menses plus tarde quando le patiente

augmentava accidentalmente su ingestion de calcium.

Ben que le syndrome alcalin de bibitores de lacte debe esser prendite in consideration in le diagnose differential, il habeva in le presente caso nulle signo de affection renal. In plus, le agentes anti-acide e le productos de lacte del regime pro ulcere non esseva prendite durante un prolongate periodo de tempore. Il es apparente que le calcium del sero montava marcatemente post solmente leve augmentos del ingestion de calcium. Ben que steroides causa un augmento del excretion fecal e urinari de calcium, tales non esseva prescribite in le presente caso, proque le symptomas dispareva promptemente post le reduction del ingestion de calcium. In plus, il habeva le contraindication relative del previe existentia de un ulcere duodenal.

Hypercalciemia deberea esser prendite in consideration in le casos de omne patientes con vage disconforto supero-abdominal. Illo deberea esser investigate promptemente in patientes con un historia de ulcere qui non responde a un appropriate therapia.

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ABSENCE OF SERUM ALBUMIN ASSOCIATED WITH RHEUMATOID ARTHRITIS * †

By M. R. SHETLAR, Ph.D., R. W. PAYNE, M.D., GEORGE STIDWORTHY, M.S., and DAVID MOCK, M.D., Oklahoma City, Oklahoma

ALBUMIN is the most abundant serum protein component in the normal human being. This major serum protein component is of obvious importance in providing a major portion of the osmotic pressure of serum; in addition, it performs important transport functions. Bennhold 1 has described two related individuals whose sera were lacking in albumin. These patients were a woman in apparently good health except for occasional slight edema, and a brother with the same defect found during a familial study.

The present report deals with studies of a patient with severe, classic rheumatoid arthritis who, in addition, exhibited a virtual analbuminemia.

CASE REPORT

A 61 year old Negro male was admitted to the Veterans Administration Hospital, Oklahoma City, in May, 1956, complaining of dyspnea and generalized body swelling. Although the edema was of recent onset (three weeks), exertional dyspnea had been present since 1949, and followed numerous episodes of pharyngitis and migratory joint pains.

Examination on admission revealed the patient to be in frank cardiac failure, with further evidence of aortic insufficiency, cardiomegaly and basilar râles, but with no hepatic enlargement. Blood pressure was 118/40 mm. of Hg. Peripheral joint deformities typical of moderately advanced rheumatoid arthritis were present.

The patient responded adequately to rapid digitalization, losing 20 pounds in four days, and was subsequently satisfactorily maintained on 0.15 mg. of digitoxin daily. A total serum protein concentration of 4.7 gm. per 100 ml., with an albumin component of only 0.6 gm./100 ml. (determined by the Howe Na2SO4 salting out procedure), was discovered in the initial laboratory work. Paper electrophoresis studies (which will be described in detail) revealed only a trace of true serum albumin.

Liver function studies (bromsulfalein, prothrombin time, thymol turbidity, cephalin flocculation, serum cholesterol and esters, and serum alkaline phosphatase) were all within normal limits with the exception of a transitory elevation of the thymol turbidity and cephalin flocculation tests on one occasion.

A needle biopsy of the liver was described by the pathologist as essentially normal. Muscle and skin biopsies were also normal. Sternal marrow samples were examined in seeking the cause of a persistent mild hypochromic anemia, and were interpreted as showing only slight erythroid hyperplasia. L. E. preparations have consistently been negative.

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Table 1

Distribution of Serum Proteins as Determined by Spinco Analytrol in Grams of Protein per 100 Ml. of Serum

| | Total | Albumin | Globulins | | | |
|---------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| | | | era | as a | 8 | 7 |
| Patient 7/17/56 | 5.18 | 0.09 | 0.19 | 0.93 | 1.11 | 2.87 |
| 2/11/58 | 6.05 | 0.07 | 0.34 | 0.94 | 1.01 | 3.70 |
| 2/24/58 | 5.32 | 0.07 | 0.30 | 0.91 | 0.84 | 3.19 |
| 2/24/58* | 5.32 | 0.00 | 0.28 | 1.06 | 1.13 | 2.84 |
| 3/18/58 | 6.95 | 0.09 | 0.37 | 1.67 | 1.02 | 3.80 |
| 8/21/58 | 5.67 | 0.05 | 0.36 | 1.12 | 0.92 | 3.22 |
| Brother 8/6/58 | 6.87 | 4.22 | 0.15 | 0.37 | 0.59 | 1.54 |
| Son 8/25/58 | 7.48 | 5.16 | 0.12 | 0.33 | 0.53 | 1.34 |
| Normal | 6.50-7.73 | 3.65-5.15 | 0.18-0.45 | 0.42-0.77 | 0.50-1.00 | 0.75-1.40 |
| Active Rheum. Arth. | 6.40-8.54 | 2.37-4.00 | 0.31-0.61 | 0.71-1.42 | 0.76-1.58 | 1.10-2.94 |

^{*} Whatman 3 MM paper; all others, Schleicher & Schuell 2043A.

An elevation of ASO titers has never been observed in this patient, but his electrocardiograms, even prior to digitalis administration, exhibited a persistent partial A-V block, with occasional ventricular extrasystoles.

Various "acute phase reactant" tests, including C-reactive protein, serum glycoprotein, seromucoid and erythrocyte sedimentation rate, were found to be consistently elevated, indicating a high degree of systemic inflammatory activity of the rheumatoid process. A test for the rheumatoid factor * was strongly positive. Following prolonged physiotherapy, the patient was discharged from the hospital in June, 1957.

He was re-admitted five months later, again in an anasarcous state after having discontinued taking his digitoxin. Approximately six weeks prior to admission he had noted increasing dyspnea, the onset of peripheral edema, and progressive abdominal enlargement. He was again found to be in severe cardiac failure and was redigitalized, with excellent response. Anemia and hypoalbuminemia were still present. No free hydrochloric acid could be obtained on gastric analysis even with histamine stimulation, and the radioactive vitamin B_{12} uptake was found to be slightly below the normal range. However, the administration of vitamin B_{12} paren-

Table 2

Distributions of Protein-Bound Hexose Among Serum Fractions in Milligrams Hexose per 100 Ml. of Serum

| | Total | Sero- mucoid | Albumin | Globulins | | | |
|---------------------|---------|-----------------|---------|-----------|-------|----------------|----------------------------------|
| | | | | Ø1 | ai | 8 | γ |
| Patient 7/17/56 | 179 | 33 | 0 | 53 | 53 | 37 33 35 | 37 |
| 2/11/58 | 190 | 30 | 4 | 47 | 78 | 33 | 28 |
| 2/24/58 | 197 | 30 27 35 | 2 | 44 | 74 - | 35 | 37 28 42 68 38 33 |
| 3/18/58 | 260 | 35 | 2 | 46 | 105 | 39 | 68 |
| 8/21/58 | 230 | - | 1 | 53 | 99 | 39 | 38 |
| Brother 8/6/58 | 127 | | 27 | 15 | 30 | 22 | 33 |
| Son 8/25/58 | 105 | - | 14 | 13 | 34 | 24 | 20 |
| Normal Range | 93-138 | 9-18 | 11-20 | 12-22 | 22-50 | 22-40 | 15-26 |
| Active Rheum. Arth. | 144-225 | 26-34 | 12-18 | 22-40 | 58-90 | 30-43 | 16-34 |

^{*} The R. A. test, Hyland Laboratories, Los Angeles, California.

terally and folic acid orally failed to induce a reticulocyte response. Intermittently the patient has been troubled by a copious, foul-odored, occasionally oily diarrhea, unassociated with nausea or any abdominal distress. Upper gastrointestinal x-ray series have not demonstrated the "puddling" characteristic of the malabsorption syn-

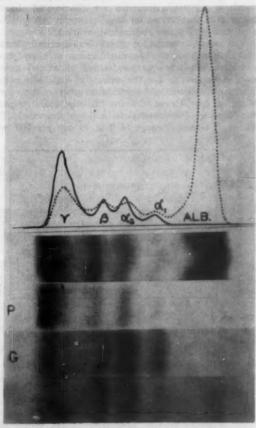


Fig. 1. Paper electrophoresis of serum of patient with analbuminemia. Strip P was stained with bromphenol blue for protein. Strip G was stained by periodic acid-Schiff reaction for glycoprotein. Arrows denote point of application. Top and bottom strips are of a normal serum stained for protein (top) and glycoprotein (bottom). Above the strips are densitometer tracings of the protein strip of the analbuminemia serum (solid line) and of the normal serum (dotted line).

drome, but the finding of essentially flat three-hour oral and normal intravenous glucose tolerance curves strongly suggests that some variant of this syndrome may be operative in this patient.

Paper Electrophoretic Studies: Numerous serum samples from this patient have now been studied over a period of two years. None of these samples has been found to contain more than a trace of albumin. The paper electrophoretic technic employed was essentially as described by Block, Durrum and Zweig,² using the Spinco hanging

strip electrophoresis cell. Both Whatman 3 MM and S & S 2043A filter paper strips were used in the study. A typical protein pattern from the patient compared with one from a normal individual is shown in figure 1. The absence of the albumin component is immediately apparent. Distribution of the serum proteins among the different electrophoretic fractions for several serum samples is shown in table 1. α_2 -, β -, and particularly γ -globulin fractions are all elevated above normal levels. However, it is noteworthy that values for these fractions fall within the range previously found for patients with active rheumatoid arthritis.

A duplicate set of patterns stained for protein-bound carbohydrate by the periodic acid-Schiff reaction is also shown. The distributions of bound carbohydrate (expressed as milligrams of bound hexose per 100 ml. of serum) among the different protein fractions are given in table 2. The amount of α -globulin is normal; however, as indicated by the protein-bound carbohydrate strip (G), the α_2 -globulin contains far more than its normal complement of bound carbohydrate. As partial explanation of this finding, the seromucoid is found to be noticeably elevated (27 to 33 mg. per 100 ml., as compared to a normal range of 9 to 18 mg. per 100 ml.). The bound

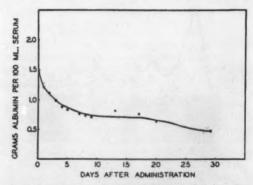


Fig. 2. Albumin content of serum of patient following administration of 67.5 gm. of human albumin (Cutter).

hexose associated with the α_2 -, β - and γ -globulins is increased above normal levels, but generally falls within the range of values for patients with active rheumatoid arthritis.³

Administration of Human Albumin: Human albumin (salt-poor) * was administered intravenously on several occasions in order to study this patient's utilization of albumin. Following administration of exogenous human serum albumin, dramatic changes in the electrophoretic patterns were observed, with the appearance of a definite albumin band. In one such treatment period, serial paper electrophoretic studies were carried out, and the results are presented graphically in figure 2. Five units (67.5 gm.) of albumin were administered on the first day of the experiment. No change in blood volume occurred, and no albumin was detected in the urine (by Heller's ring test). It would appear from these data that the patient utilizes administered albumin in a normal manner. Administration of human albumin did not appear to affect grossly the clinical status of the patient.

Immunochemical Studies: Serum albumin in this patient was determined by immunochemical means, according to the method of Chow. A value of 0.08 gm. of albumin per 100 ml. of serum was obtained by this method. On this same sample an

^{*} Generously supplied by Dr. Edwin McLean, Cutter Laboratories, Berkeley, California.

albumin level of 0.09 gm. per 100 ml. of serum was found by paper strip electrophoresis. An aliquot of this sample was also fractionated by column electrophoresis, using cellulose powder and veronal buffer, pH 8.6, 0.05 M. By this technic, 1.2% of the total serum protein was found to be albumin (corresponding to .08 gm. of albumin per 100 ml. of serum); only this fraction produced a positive test for albumin with human albumin antiserum.

Studies of Physical Properties: Total osmolarity was determined on a sample of serum by freezing point depression with the Fiske Osmometer.* A value of 284 osmols per liter was obtained, as compared to normal values of 280 to 290 osmols per liter determined with the same instrument. An estimation of the average particle weight as determined with the light-scattering flame photometer was made on one sample, and a value 1.50 times normal was found for the serum of the patient.

Familial Studies: Electrophoretic studies were made of the only available living close relatives of the patient, a brother and a son (tables 1 and 2), and essentially

normal protein patterns were observed in both cases.

DISCUSSION

Since no evidence of liver abnormalities was found by liver function and liver biopsy studies, it would appear that this individual exhibits a specific hepatic defect, i.e., the lack of the necessary enzyme system required to synthesize serum albumin. Further indication that a defect in formation of serum albumin is involved is the apparently normal utilization of exogenous human albumin. In the case studied there is little evidence as to whether this defect is congenital or acquired. The two relatives studied show no signs of the defect, but more extensive familial studies are indicated before any conclusion may be drawn.

Except for the striking absence of albumin, the paper electrophoretic protein and glycoprotein patterns of the present case are similar in all respects to those of patients with active rheumatoid arthritis. Although a decrease in serum albumin invariably accompanies acute rheumatoid arthritis and other severe inflammatory conditions, complete absence of serum albumin has not previously been found to be associated with these conditions. However, the possibility still remains that this case may represent a rare variant of rheumatoid arthritis.

SUMMARY

A patient with a striking deficiency of serum albumin has been described. In addition to analbuminemia, this patient suffers from severe rheumatoid arthritis and rheumatic heart disease. Paper electrophoretic studies of the proteins and glycoproteins indicate that elevations of the carbohydrate-rich globulins and of seromucoid are present in the serum of this patient; these concentrations, however, fall within the range of those found in patients with active rheumatoid arthritis. Human serum albumin administered to this patient was apparently utilized at a normal rate.

SUMMARIO IN INTERLINGUA

Es describite studios in un masculo negre de 61 annos de etate con un frappante deficientia de albumina seral. A parte le analbuminemia, le patiente habeva sever arthritis rheumatoide e rheumatic morbo cardiac. In le curso de un periodo de duo annos, su sero—secundo determinationes per electrophorese a papiro—nunquam con-

^{*} Fiske Associates, Hathorne, Massachusetts.

tineva plus que un tracia de albumina. Le maximo esseva 0,09 g per 100 ml, le minimo absentia complete. Studios immunochimic de un specimen verificava le basse valor obtenite per le methodo electrophoretic. Elevationes del glycoproteinas e del seromucoide in le sero esseva simile a lo que es incontrate in sever arthritis rheumatoide. Le usual tests del function hepatic esseva intra le limites del norma. Post administrationes de albumina human, nulle albumina esseva trovate in le urina, e le nivello del albumina in le sero descendeva de maniera normal. Le conclusion es que il se tractava in iste caso de un defecto metabolic, i.e., le patiente non habeva le capacitate de synthetisar albumina seral.

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IDIOPATHIC HYPOPARATHYROIDISM: A CLINICAL DISCUSSION WITH A CASE REPORT*

By Louis J. Acierno, M.D., Brooklyn, N. Y., and E. Thaler, M.D., Glen Oaks, Long Island, N. Y.

WITHIN recent years there have been increasingly numerous reports of patients with idiopathic hypoparathyroidism. This is probably because a higher index of suspicion exists today, and the possibility that the serum calcium may be low is now entertained in all individuals with unusual muscle contractions, convulsions or subcapsular cataracts.

The present case is reported because, although the patient was under medical observation for five years and had all the manifestations of the disease during that time, no diagnosis was made during the period.

CASE REPORT

The patient, a 50 year old white male of Italian descent, was admitted to Long Island College Hospital via ambulance on August 17, 1956, following an episode at

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From the Long Island College Hospital.
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home during which he lost consciousness for two minutes and his arms and legs became rigid.

The evening before admission the patient had eaten a spicy Italian dinner. The following morning he awoke with a severe headache, and complained of general malaise and chilly sensations. His temperature was 38.3° C. He then vomited and passed a diarrheal stool which was described as being watery, greenish yellow and foul-smelling, his malaise becoming progressively worse. During the day, numbness and tingling sensations developed in the arms and hands, and he then noted that his hands and feet became fixed and rigid in the position of carpopedal spasm. On trying to get out of bed that afternoon he lost consciousness for about two minutes, presumably falling to the floor. No epileptic type of convulsive seizure was noted by his wife during the period of unconsciousness.

Past History: The patient had apparently been in perfect health until 1947. For the next two years, while working as a tailor, he began to notice progressive loss of visual acuity, and easy fatigability and irritability. The irritability was characterized by "jumpiness" and emotional instability. In 1949 he changed his occupation to outdoor work as a longshoreman because of failing vision.

In 1950, when he was 46 years old, the patient first consulted an ophthalmologist; he hoped that correction of his progressive diminution in vision would eliminate his irritability. A diagnosis of bilateral cataracts was made, but surgery was deferred for unknown reasons. Subsequently he was treated by a local physician with vitamins and "sex hormones" for a short time, but without success. In 1952 he was hospitalized by the ophthalmologist for removal of the subcapsular cataracts. While he was in the hospital he was referred to one of us (L. J. A.) for a diagnostic survey. The pertinent findings on this survey were as follows: (1) calcification of the sella turcica on skull films, and changes in the right iliac bone which were interpreted by the radiologist as being consistent with Paget's disease; (2) serum calcium, 5.21 mg.%; serum phosphorus, 3.6 mg.%; alkaline phosphatase, 6.8 Bodansky units; acid phosphatase, 3.1 King-Armstrong units; urinary calcium excretion in 24 hours, 208.5 mg.

The diagnosis of a deranged calcium metabolism was entertained, but the patient did not allow further studies to be made. Nevertheless, he was given calcium and multivitamins orally. In addition, arrangements were made to have his wife give him a daily intramuscular injection of 200,000 units of vitamin D. These directions were followed in a rather sporadic fashion and for several months only.

Within the next year a bilateral iridectomy was performed. Postoperatively, and up to the time of admission to the Long Island College Hospital, the patient noted progressive weakness, frequent frontal headaches, and numbness and tingling of the upper extremities, as well as twitching of the eyelids. Upon lifting objects with his hands he frequently developed spasticity of the fingers. He also experienced intermittent episodes of three to four watery bowel movements a day, these diarrheal episodes lasting for several days at a time. On the morning of the day of admission the symptoms described above in the present illness had been worse than usual.

There was no history of thyroid or neck operations, and the rest of the past history was noncontributory.

Social History: There was no history of excessive usage of alcohol or tobacco. Family History: A twin brother died of heart disease at the age of 32, and was known to have had chorea.

The patient became quite nervous, and worried a good deal over his inability to support his family properly. Because he lacked strength and drive, he was able to work only a little at odd jobs. At times he felt that he was "going out of his mind." He had the idea (probably in the nature of a "Zwangsidee") that he wanted to kill his wife and three children, whom he loved and still loves.

TABLE 1A

| and the state of t | Before Admission August, 1952 | During Hospital Stay | | |
|--|--|--|--|--|
| V and | | Pre-therapy August, 1956 | Post-therapy September, 1956 | |
| Serum calcium Serum phosphorus Alkaline phosphatase Acid phosphatase Urinary calcium (24 hr.) Blood urea nitrogen Urea Fasting blood sugar Total protein A: G ratio Cholesterol Cholesterol esters CO ₃ combining power | 5.21 mg. % 3.6 mg. % 6.8 B.U. 3.1 KA 208.5 mg. % | 5.4 mg. % 7.2 mg. % 5.6 B.U. 52 mg. % 11 mg. % 23.5 mg. % 141 mg. % 7.4 gm. % 4.7 : 2.7 gm. % | 8.8 mg. % 5.6 mg. % 5.6 B.U. 82 mg. % 20.3 mg. % 43.5 mg. % 62.2 gm. % 4.5:1.7 gm. % 208 119 68.8 vol. % | |

Examination on Admission: The patient was a well developed, mildly obese 52 year old white male who, though not apparently in acute distress, seemed anxious about his condition. Temperature, 102° F.; blood pressure, 90/60 mm. of Hg; respiration, 20; pulse, 90. No abnormalities of the skin were seen. The hair was thick, black and coarse. There were transverse ridging and coarseness of the nails. Peripheral pulsations were equal and normal bilaterally. There was no peripheral lymphadenopathy. A bilateral iridectomy status was noted. The thyroid was not palpable, and no operative scars on the neck were seen. Oral hygiene was poor. The lungs were clear to percussion and auscultation. Respiratory excursions were normal and equal bilaterally. There was no cardiomegaly on percussion. Regular sinus rhythm was present. No murmurs were heard. The heart sounds were distant; and A2 equaled P2. The liver was palpated two fingerbreadths below the right costal margin and it was not tender. No other abdominal masses were present. A 4 plus Chvostek's sign was elicited bilaterally; the patellar reflexes were hypoactive bilaterally. There were no other abnormal neurologic signs. The extremities were normal.

TABLE 1B Laboratory Studies

| Hemogram: RBC—4.65 million Hb.—14.6 gm. | Serologic tests for lues: Mazzini—2+ VDRL—negative | X-ray studies: Chest—concentric hypertrophy of left ventricle Pelvis—coarsening of trabeculae of | |
|--|---|--|--|
| Hematocrit 25 WBC—4,650 N.—68% Lymphs.—30% | Mosenthal test: Normal concentration up to 1.020 | entire right half of pelvis—compatible with Paget's disease Skull—Calcification of anterior an posterior clinoid—otherwise norma | |
| Sed. rate—9.5 mm./hr. | Radioactive iodine uptake: Within normal limits (23%) | | |
| Urinalysis: A. On admission occ. hyaline and granular casts B. Subsequent studies 1. All within normal limits | PSP and urea clearance tests: Both within normal limits | ECG: Normal with no significant change after 40 c.c. of 10% Ca gluconate I.V. | |
| | Gastric analysis: No abnormalities | Ellsworth-Howard test: | |
| Stool examinations: 1. No increase in neutral fats | Glucose tolerance curve: Within normal limits | See fig. 1. | |
| Negative for ova, parasites and occult blood BSP: retention after 45 minutes | EKG on admission: Low voltage throughout significantly prolonged QT. QT of 0.44 at rate of 72/min. (Normal, 0.395) | or the second | |

Course in Hospital: On admission the patient was given 20 c.c. of 10% calcium gluconate intravenously. In addition, Kaopectate was given for the diarrhea, and no further difficulty was experienced with this. No other therapy was given until all diagnostic procedures had been completed, which was accomplished within the first week of hospitalization. Table 1 (A and B) is a compilation of the laboratory data obtained before admission, during the diagnostic phase of the patient's hospital course and subsequent determinations of pertinent studies until discharge.

On August 25, 1957, the eighth hospital day, the appropriate therapeutic regimen was instituted. This consisted of the administration of a low phosphorus diet (which excluded milk, milk products, and high phosphorus vegetables). In addition, the patient was given: (1) calcium lactate, 10 gm. orally daily; (2) dihydrotachysterol (AT 10), 1 c.c. (containing 1.65 mg. of the sterol) intramuscularly three times daily; (3) aluminum hydroxide, three times daily (table 2). Within one week he felt subjectively improved. Subsequently there was definite correlation between his clinical improvement and the serial serum levels of calcium and phosphorus, as well as with the Sulkowitch reaction and the Chyostek sign.

On August 31, 1957, the serum calcium was 5.6 mg.%; inorganic phosphate, 6.4 mg.%. On September 5, 1957, the serum calcium was 5 mg.%, the inorganic phosphate 6.6 mg.%. At this time the alkaline phosphatase was 5.5 Bodansky units.

TABLE 2

| | Interim | | | |
|---|--|--|--|--|
| Therapy | 8-25-569-7-56 | 9-7-56-9-29-56 | | |
| AT 10 Calcium lactate Aluminum hydroxide Low P diet | 1 c.c. t.i.d. 10 gm. daily 8 c.c. t.i.d. | 2 c.c. t.i.d. 16 gm. daily 8 c.c. t.i.d. | | |

Thus on September 7, 1957, the dosage of AT 10 was increased to 2 c.c. three times daily, and the oral calcium gluconate to 4 gm. four times a day. By September 10, 1957, the intensity of the Chvostek response was reduced to 1–2 plus, and the patient slept better, felt more relaxed, and was in much better spirits than on admission. The serum calcium was still only 5.4 mg.%, the inorganic phosphate, 5.6 mg.%.

On September 13, 1957, the serum calcium had risen to 7 mg.% and the inorganic phosphate to 5.9 mg.%. The Chvostek sign was 1 plus and soon thereafter practically disappeared, so that a slight twitch was all that remained of the sign.

On September 18, 1957, for the first time, the daily Sulkowitch test showed a 1 plus response. The patient continued to feel stronger and less nervous, and the Sulkowitch test continued to reveal a trace to 1 plus reaction. On September 24, 1957, the serum calcium rose to 8 mg.% and the AT 10 was reduced to 1.65 mg. (1 c.c.) three times a day. On September 27, 1957, the serum calcium was 8.8 mg.%; the inorganic phosphate, 5.6 mg.%, and the alkaline phosphatase, 6 Bodansky units. The Sulkowitch test was 2 plus, and the 24-hour urinary calcium excretion was 82 mg. From this point on, the patient made steady progress clinically, and the laboratory data rapidly improved, to reach a normal status. In particular, there was a progressive rise in serum calcium, with a concomitant fall of inorganic phosphate. The patient was discharged on the forty-third hospital day and was advised to adhere to the following regimen: (1) vitamin D, 300,000 units daily intramuscularly; (2) calcium gluconate, 6 gm. daily by mouth; (3) a low phosphorus diet; (4) phosphorus-free multivitamins. He was instructed to return at weekly intervals so that treatment could be adjusted in accordance with his symptoms, and to report the results of the daily Sulkowitch's test as performed by him.

Subsequently, fetal parathyroid transplant surgery was performed.

DISCUSSION

The parathyroid glands have as far as is known only one known function, the production of parathyroid hormone.¹ The stimuli for the elaboration of this hormone are said to emanate from two basic mechanisms, which have been called the "calciostat" and "phosphostat" mechanisms. The "calciostat" mechanism is probably the more important, and is concerned with homeostatic regulation of serum calcium. There is much experimental evidence to show that if the serum calcium concentration is decreased, there is an increased output of parathyroid hormone. This mechanism forms the basis of the calcium tolerance test.

It is generally believed, though not definitely proved, that the "phosphostat" mechanism is called into play only when the serum phosphorus level has increased without any simultaneous alteration of the serum calcium. It forms the

basis of the phosphorus deprivation test.

The parathyroid hormone has two fundamental physiologic effects.²⁻⁸ One is a primary proteolytic action on decalcified bone matrix; the other concerns itself with the regulation of phosphorus concentration in the body economy. The proteolytic action is a subsidiary one, and is believed to be exerted via osteoclast stimulation by the hormone. The initial and most fundamental action of the hormone is probably increased phosphorus diuresis. How this is accomplished is unknown, though most students of the problem feel that it is due to a specific depression of the capacity of the tubules to reabsorb phosphorus. As there is progressive loss of phosphorus through the renal pathway, the serum calcium level must change in a direction to satisfy the solubility product of Ca and PO., so that normal saturation is reached. The sequential scheme of events is thus as follows: hyperphosphaturia, which lowers the serum P level, followed by a compensatory rise in serum calcium concentration, which in turn results in hypercalciuria. The increased demand for calcium is supplied from exogenous sources through the gastrointestinal tract. If this is not sufficient to satisfy the demand, then the bones are tapped for the necessary calcium, this serving secondarily as a calcium reservoir.

When there is insufficient—or complete absence of—parathyroid hormone, there is increased tubular reabsorption of phosphorus. As the serum phosphorus concentration rises, the solubility product of Ca and PO₄ is exceeded, with resultant supersaturation, so that there is a decreased demand for calcium and phosphorus from the bones. To maintain the physiologic saturation point of the solubility product, the serum calcium concentration decreases. This lowered serum calcium level is the keynote to the major manifestations of hypoparathyroidism.⁹ Since less calcium is presented to the kidneys for excretion, a pro-

gressive hypocalciuria ensues.

Tetany is by far the most dramatic abnormality in this disease. It has been present in at least 78% of the reported cases. 10,11,12 In due time—and sometimes only acutely, in an explosive fashion—varying degrees of tetany will bring the patient to a physician. This increased neuromuscular excitability is dependent upon the concentration of serum calcium, and may involve smooth, skeletal or cardiac muscle. Peripheral muscular spasm with paresthesias, cramps or twitchings of the muscles of the extremities or facial muscles may be the only manifestation. If latent, tetany may be elicited by Chvostek's, Trousseau's

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or Erb's maneuvers. At times the bronchial muscles may be involved, producing the full-blown picture of bronchial asthma.¹ Death has been reported during an acute phase of tetany due to asphyxia from laryngeal spasm.¹ Acute surgical abdominal lesions may be simulated as a result of tetany of the gastro-intestinal musculature.¹ The hypocalcemia may result in prolongation in the electrocardiogram of the QT interval, with or without flattening of the ST segment. This is not a constant finding; however, when present, it constitutes important ancillary (though not specific) evidence for hypoparathyroidism.¹³

The incidence of generalized convulsions is reported as 52%. Dilepsy may be the only symptom, and is often misdiagnosed as idiopathic. Although it is true that the incidence of hypocalcemia is quite low in idiopathic epilepsy, the frequency of convulsive seizures as an accompanying or single manifestation of idiopathic hypoparathyroidism is significant enough to warrant calcium and phosphorus studies in all individuals with epilepsy. Hypocalcemia, again, is probably the basic precipitating mechanism for the convulsive seizures, though McQuarrie advanced the opinion that an additional factor is probably edema of the brain, with consequent disturbance in the surface function of the brain cell membrane. 14, 15, 16 Actually, abnormal electrical potentials have been reported on the basis of electroencephalographic studies. 17, 18 These have been described as a diminution or disappearance of the slow alpha rhythm in the frontal, occipital and parietal leads, or as an increase in the amplitude and constancy of the beta rhythm, as well as an increase in waves of low frequency. 9, 10, 14, 81 Such changes have been described by Taubenhaus 15 and Ordiz.18 Our patient, even after hyperventilation, failed to reveal any specific changes in the electroencephalogram.

Another central nervous system manifestation may be papilledema.^{19,20} Von Ommen reports its incidence as 14%, with the statement that it usually disappears with treatment.¹⁰ Obviously this finding, especially if associated with epilepsy, may lead to the mistaken diagnosis of a brain tumor. The underlying physiologic abnormality causing this sign remains to be delineated. Grant felt, on rather scanty evidence, that the hypocalcemia, per se,²¹ is responsible by directly producing generalized cerebral edema.

Ectodermal lesions may be quite pronounced, due to the chronicity of the illness. These lesions may involve the skin, hair, teeth, nails and eye lenses.^{22, 28, 24} Cataracts are a very common complication of hypoparathyroidism. It is generally believed that they are due to the hypocalcemia (with ciliary spasm), rather than to the convulsions, as some authors have suggested. This is quite likely, since cataracts are seen in other types of disorders with hypocalcemia, such as sprue, etc.

Horizontal grooving of the nails, with less conspicuous longitudinal grooving, is said to be typical. Other changes reported include atrophy of the nails, occasional association with moniliasis, and, at times, complete loss of nails.

The type of dental defect that may occur depends upon the age at which hypoparathyroidism develops. The defects are primarily those of enamel formation, but they may also involve the temporal development of the deciduous teeth as well as the permanent teeth. Thus, the dental manifestations may include aplasia or hypoplasia of the teeth in varying degrees, and in various portions of the tooth itself.²⁵ This lack of calcification has been explained as being due

to a relative ineffectiveness of the local calcifying factor in the presence of a high serum phosphorus and a low serum calcium.¹

Patchy thinning of the scalp hair as well as absent pubic and axillary hair has been reported.²²

The skin changes in idiopathic hypoparathyroidism are quite varied. These may consist of a dry and scaly skin, the lesions of exfoliative dermatitis, pigmentation resembling chloasma gravidarum, and dermatitis herpetiformis. Sev-

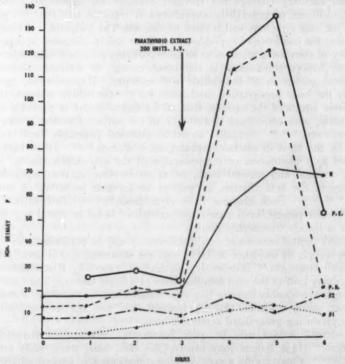


Fig. 1. Since the patient developed 3 by 2 cm. erythema with no induration on a skin test with 0.2 c.c. of parathyroid extract (Lilly), the 200 U.S.P. units were given in divided doses over a period of 30 minutes. Chlor-trimeton, 25 mg. intramuscularly, was given just before the administration of the hormone. The patient was in a fasting state. The results have been superimposed on those established by Albright in two patients with known pseudo-hypoparathyroidism (#1 and #2), normal response (N), and an established case of idiopathic hypoparathyroidism (PR). Compare these results with those in our patient.

eral cases have been reported of the association of idiopathic hypoparathyroidism with Addison's disease, including the pigmentation seen in the latter disease. Other endocrine disorders are seldom found and, when present, have been shown to be purely coincidental.^{26, 27, 28} Papadatos presents evidence that suggests the amelioration of the hypoparathyroid effects when adrenal insufficiency supervenes.²⁹

Roentgenologically, the most significant lesions have been cerebral calcifi-

cation, especially in the region of the basal ganglia.⁸⁰ These changes are believed to be due to deposition of a basophilic homogenous material in and about the media and adventitia of the smaller cerebral arteries, followed by calcification of these deposits. These calcifications are an important ancillary finding, but in themselves are not pathognomonic of idiopathic hypoparathyroidism, and have been described in chronic lead poisoning, tuberculous meningitis, idiopathic epilepsy, tuberous sclerosis, and mental deficiency states, to name but a few of the entities.^{81–80}

In establishing the diagnosis, most students of the problem insist that an elevated serum phosphorus level constitutes an essential criterion. This would rule out other conditions in which hypocalcemia occurs, such as the steatorrheic syndrome, rickets or osteomalacia. Hyperphosphatemia and hypocalcemia may also occur in prolonged renal insufficiency, but there is a lesser degree of hypocalcemia for the same degree of hyperphosphatemia. Moreover, appropriate laboratory data can be utilized to indicate renal impairment, per se.

Another common cause of tetany, besides hypocalcemia, is alkalosis, and this too must therefore be ruled out. By far the most common precipitating factor for alkalosis is hyperventilation, usually the result of some emotional disturbance.

A definitive diagnosis can be established by the Ellsworth-Howard test.^{87, 88} This test can discriminate especially between true primary hypoparathyroidism and pseudohypoparathyroidism. This latter syndrome, first described by Albright et al. in 1942, has the same symptomatology, physical signs and chemical findings as those of hypoparathyroidism.⁸⁹ Its cause is lack of response to parathyroid hormone, rather than a lack of the hormone. With the utilization of the primary phosphodiuretic effect of parathyroid hormone, 2 c.c. of parathyroid extract are injected intravenously into the fasting subject. The total urinary phosphorus excretion three hours later is compared with the amount found in the urine for the three hours before the extract was given. The results obtained in our patient are seen in figure 1 and are compared with the results of Albright et al.

TREATMENT

It is obvious from the previous discussion that the most important point in the management of this disease is the correction of the hypocalcemia. Since the parathyroid glands are unable to perform their function in this regard, it would seem, on theoretic grounds, that replacement therapy with parathyroid hormone itself should be the best corrective measure. Clinically, however, the administration of the hormone alone has its drawbacks. (1) It is very expensive; (2) it often causes a local reaction; (3) in due time it loses its effectiveness because of antibody formation.

Calciferol has two main actions: it increases calcium absorption from the gastrointestinal tract, and also enhances the elimination of phosphorus by increasing its rate of filtration by the glomeruli. The sterol is active orally, and does not lead to antihormone formation.

When calciferol is given to an individual with hypoparathyroidism, the increased absorption of calcium leads to an increased serum calcium level and increased urinary excretion of calcium, with a concomitant decrease in fecal

calcium excretion. There is, in addition, increased absorption of phosphorus from the gastrointestinal tract which, in turn, leads to elevated serum levels of this mineral. Finally, calciferol also causes a slightly increased urinary excretion of phosphorus which tends to counteract the increased serum concentration. The net results in the serum are an increased concentration of both calcium and phosphorus, as a consequence of which the solubility product of these is approached, so that there is a decreased need for these minerals in the serum, and thus a compensatory restoration of their levels to normal.

Perhaps the most effective agent is dihydrotachysterol. This was introduced as AT 10 ("antitetanisches Preparat Nr. 10"), and is a photochemical derivative of ergosterol. It has the same actions as calciferol except that it has a greater phosphorus diuretic effect, and in this respect more closely resembles parathyroid hormone than does calciferol or vitamin D. In addition, it causes less

inhibition of parathyroid activity.

The patient should be shown how to use the Sulkowitch test, and how to regulate this medication by its results. Early in the course of treatment the patient is asked to perform the test and to correlate the results with ours. By the time he is ready for discharge he should be fully capable of regulating his medication and understand the importance of such regulation.

In conclusion, certain aspects of this disease brought to our attention factors

which we feel should be emphasized.

Idiopathic hypoparathyroid disease may in reality be a rare disorder, but certainly it is fairly simple to put a drop of Sulkowitch reagent in the urine of every so-called idiopathic epileptic, psychoneurotic or asthmatic patient, patients with convulsive episodes, paresthesias, cramps, abdominal pain, cataracts, hair loss, exfoliative dermatitis, etc.

The manifold disturbances where a calcium deficiency might play a role would be too numerous to mention. Those cases exhibiting less than a trace reaction would then be deserving of further and more extensive study. With very rare exceptions, the Sulkowitch test is negative only if the serum calcium level is below 7 mg. per 100 c.c. (the renal threshold). The routine employment of this test may well disclose an unsuspected prevalence of hypocalcemia as a factor in many disease entities.

SUMMARIO IN INTERLINGUA

Es reportate un caso de hypoparathyroidismo idiopathic que illustra certes del aspectos typic de iste disordine e etiam le methodos usate in su diagnose.

Hypoparathyroidismo idiopathic es le complexo de symptomas que resulta del

absentia de hormon parathyroide sin ulle demonstrabile base etiologic.

Quando le hormon parathyroide es quantitativemente insufficiente o completemente absente, il occurre un augmentate reabsorption tubular de phosphoro. Isto initia un catena de alterationes biochimic que resulta finalmente in hypocalciemia e hyperphosphatemia. Le puncto cardinal inter le manifestationes de hypoparathyroidismo es le reducite nivello seral de calcium, con le concomitante augmento del excitabilitate neuromuscular que pote afficer musculo skeletic, musculo lisie, o musculo cardiac e que assi produce le varie grados e formas de tetania. Alterationes additional que pote sed non debe esser relationate con le nivello de calcium in le sero occurre in le systema nervose central, le pelle, le capillos, le dentes, le ungulas, e le lentes ocular.

Ab le puncto de vista roentgenologic, le lesiones le plus significative ha essite varie formas de calcification cerebral, specialmente in le region del ganglios basal.

In establir le diagnose, le constatation de elevate nivellos seral de phosphoro es essential. Le diagnose definitive pote esser establite per medio del test de Ellsworth-Howard.

Le plus importante aspecto del therapia in casos de iste morbo es le correction del hypocalciemia. Hormon parathyroide, calciferol, vitamin D, o AT 10 pote esser usate. AT 10 es le agente le plus efficace.

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CHRONIC MYOSITIS FIBROSA: REPORT OF A CASE *

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Although acute myositis is one of the conditions most commonly encountered by the physician, the chronic and generalized forms are more unusual. Of these, chronic generalized myositis fibrosa is a distinct rarity. First described in 1895 by Janicke, in 1951 Stewart and Macgregor 2 could find only 11 authenticated cases, to which they added a twelfth.

The disease is insidious in onset, beginning most frequently in the lower extremities. Stiffness and clumsiness are usually the first complaints, without pain, fever or other signs of constitutional "illness." Induration of the affected muscles spreads until the whole muscle belly becomes involved. This progresses to other voluntary muscles, usually sparing the sphincter and facial muscles. Absence of skin involvement and constitutional disturbance distinguish the disease from dermatomyositis.

The histologic picture is characterized by hyaline degeneration, sometimes with hydrops, loss of cross striation and variation in size of the muscle fibers, with marked increase in fibrous tissue. The muscles are firmer than usual to the touch, and cut with increased resistance. They appear to be lighter than normal, often having a grayish tint. Round cell infiltration may or may not be present.

The creatine content of muscles is reduced, as is the creatine tolerance. Schwab s found creatinuria to be a notable feature of the disease, more than 40% of creatine being excreted unchanged within 48 hours after the ingestion of this material.

In about half of the reported cases the disease had begun in childhood, the oldest being 53 years. Its progress may be interrupted by periods of remission, but treatment on the whole has been ineffective. Eventually weight loss and general deterioration set the stage for intercurrent infection, which is the usual terminal event.

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CASE REPORT

A 61 year old white male laborer was admitted to Robert Packer Hospital on June 11, 1958. He had suffered from recurrent pain in the left foot for about eight years. In 1952, on a previous admission to this hospital, this had been attributed to osteoarthritis and pronated feet. At that time, however, a circumscribed lytic



Fig. 1. Gross appearance of calves.

lesion at the distal end of the first left metatarsal was reported by the radiologist as being "consistent with gout." However, the patient's blood uric acid being only 3.1 mg.%, this consideration was abandoned.

On the present admission he called attention to a hard lump in the left calf muscles which had been developing for two years, and a newer, smaller induration and swelling in the right calf of more recent origin. The calf muscles on the left were tremendously enlarged, reminiscent of those seen in pseudohypertrophic muscular dystrophy, and had a feeling of brawny induration (figure 1). They were not tender.

Pronounced wasting of the muscles of the upper extremities was apparent; muscle grading technics demonstrated weakness in nearly every muscle in the body.

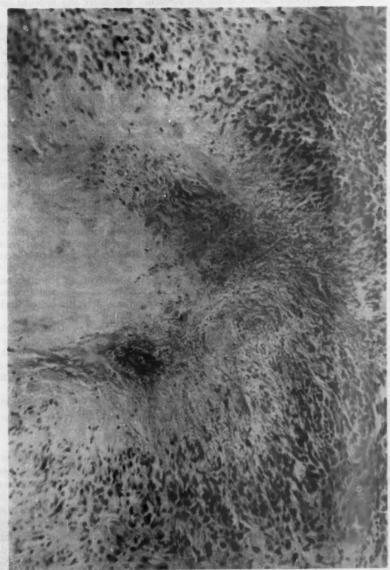


Fig. 2. Histologic appearance of muscle (left gastrocnemius).

There was a cystic swelling at the base of the right thumb and a subcutaneous nodule was noted on the extensor surface of the left forearm. The latter was removed for

biopsy and reported as a rheumatoid nodule.

Physical examination revealed a stiff-legged gait of a shuffling character. Blood pressure, 110/65 mm. of Hg; pulse, 80 and regular. There was stiffness and the range of motion in the cervical and thoracic spine was restricted. Other physical findings were not remarkable. A search for tophi was unavailing. Laboratory reports were as follows: Urine: acid; specific gravity, 1.020; no albumin, sugar or formed elements. Blood count on June 12, 1958: hemoglobin, 16.2 gm.; red blood count, 4,950,000; white count, 20,400; segmented cells, 79; lymphocytes, 13; mononuclears, 2; stabs, 1.5; eosinophils, 5.

On June 17 the white blood count was 15,250, with a similar differential. Fractional gastric analysis showed adequate free acid in all specimens. The fasting blood sugar was 88; serum uric acid, 5.2; erythrocyte sedimentation rate, 25 mm./hr.; C-reactive protein, 4 plus. The result of the serologic test for syphilis as performed with the Venereal Disease Research Laboratory (VDRL) antigen was negative.

The preliminary urine contained no creatine, but in 48 hours after the ingestion of 1 gm. of this substance the patient excreted 882 mg. of creatine in the urine.

Results of x-ray examination were as follows: Films of the feet showed cystic radiolucent areas in the heads of both first metatarsals; these were noticed also in the hands and wrists, particularly the first metacarpal and the distal left radius. Films of the cervical spine showed severe degenerative arthritis; the chest films showed diffusely scattered linear and minute nodular fibrotic densities which were interpreted as silicosis.

On June 13, 1958, the nodule on the left forearm was removed and a section for biopsy taken from the left gastrocnemius muscle. In the process a cyst was encountered in the belly of the calf muscle and drained of approximately 100 c.c. of fluid.

This cyst fluid contained many cells, but culture proved sterile.

The pathologic report on the muscle tissue was as follows: "The striated muscle showed marked changes characterized by a central zone of fibrinoid necrosis surrounded by palisading epithelioid cells and other chronic inflammatory cells. Outside of this area the muscle showed cystic degeneration with variation in the size of muscle fibers and loss of striation. There was marked atrophy of muscle fibers with numerous foci of fibrosis and deposition of collagenous fibrous tissue" (figure 2).

Section of the subcutaneous nodule from the forearm revealed a similar patho-

logic picture and was interpreted as a subcutaneous rheumatoid nodule.

DISCUSSION

This case presents many of the characteristic features of myositis fibrosa. The insidious onset, with muscle stiffness involving the lower extremities, resembles other reported cases; this man's pain is dissociated from the muscular dyscrasia, being attributed to his joint disease.

The histologic changes, which include variation in size of muscle fibers and increase in the amount of fibrous tissue, are consistent with the changes noticed in other reported cases. Although Schwab 8 lists hydrops of muscle tissue among the degenerative changes, no such massive cysts as seen in our case are described.

The failure of muscles to metabolize creatine, as indicated by its excretion in the unchanged form, certainly suggests widespread muscular disease; this phenomenon has been repeatedly described in this condition. The only other primary chronic myositic diseases mentioned by Somers 4 are dermatomyositis and myositis ossificans progressiva. The former can be eliminated in this case

by the complete absence of skin manifestations, just as the latter is easily excluded by the absence of radiologic evidence of calcification in the muscles.

There are some interesting and unusual features in this case beyond the cystic degeneration of the calf muscles. If we are correct in assuming that this is a true myositis fibrosa, at 59 years it is the oldest onset on record. Previously Somers has claimed this record for his case, whose onset was at 53 years.

The association of rheumatoid arthritis with myositis fibrosa in this case is worthy of comment. Schwab believed that from a histologic standpoint these cases fall within the rheumatoid arthritic syndrome.

Somers disagrees with this position, maintaining that the afebrile nature and lack of evidence of infection indicate a degenerative rather than an inflammatory disease. The present case, with a typical rheumatoid subcutaneous nodule, accelerated sedimentation rate and C-reactive protein in high titer, would tend to substantiate Schwab's opinion. Ornsteen 6 cites Pemberton's opinion that the pathologic process implied is really a part of and belongs to the rheumatoid or arthritic syndrome, and that there is every reason to believe that it springs from the same causative factor as does rheumatoid arthritis, and should be regarded as an expression in the muscular tissues of the same underlying process.

Prognosis and Treatment: As previously mentioned, the downhill course of this disease may be interrupted by remissions. Burton et al.⁶ reported a case that showed marked improvement during a prolonged remission.

While treatment is generally reported as ineffectual, Blau ⁷ reported considerable subjective relief with the consistent use of glycocoll in large doses.

SUMMARY

- 1. A case with many of the features of generalized myositis fibrosa is reported.
- 2. Although atypical in some respects, the histologic picture and the diminished creatine tolerance are consistent with such a diagnosis.
- 3. Unusual features of this case are (a) the age of onset, (b) cystic degeneration of the muscles, and (c) the simultaneous occurrence of typical subcutaneous rheumatoid nodules.

SUMMARIO IN INTERLINGUA

Chronic myositis fibrose es un condition distinctemente inusual, characterisate ab le puncto de vista clinic per rigiditate e induration de musculos voluntari e ab le puncto de vista histologic per degeneration hyalin de musculo, perdita de striation transverse, variation in le dimensiones del fibras muscular, hydropisia, e marcate augmentos de histo fibrose. Un reducite tolerantia pro creatina es un aspecto essential del syndrome. Inter le previemente reportate casos, le plus vetule patiente habeva un etate de 53 annos.

Le presente caso es illo de un homine de 61 annos de etate. Le patiente exhibiva un tableau histologic perfectemente de accordo con le characteristicas del morbo. Su excretion de un dose experimental de creatina amontava a 88 pro cento intra 48 horas. Le patiente etiam monstrava multe aspectos que poteva suggerer le presentia de arthritis rheumatoide. Un nodulo subcutanee excidite ab le superficie del extensor bracial esseva interpretate como un nodulo rheumatoide, e le test pro proteina Creactive esseva fortemente positive.

Le caso, ben que atypic de myositis fibrose in certe respectos, presenta le tableau histologic e le reducite tolerantia pro creatina que characterisa le morbo. Aspectos inusual es le etate del patiente, le degeneration cystic de musculo, e le association con arthritis rheumatoide.

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SARCOIDOSIS WITH PANHYPOPITUITARISM AND **DIABETES INSIPIDUS***

By Joseph R. Nora, M.D., John M. Levitsky, M.D., and HYMAN J. ZIMMERMAN, M.D., F.A.C.P., Chicago, Illinois

PITUITARY insufficiency is a rare complication of sarcoidosis.^{1, 2} Diabetes insipidus due to infiltration of the posterior lobe of the pituitary or hypothalamus has been reported by Tillgren,⁸ Longcope ⁶ and others. Anterior pituitary insufficiency has been reported even less frequently.5, 6 The coexistence of diabetes insipidus and anterior pituitary dysfunction, as reported below, is a unique complication of sarcoidosis. The patient described illustrates some of the endocrine interrelationships involved in diuresis and antidiuresis.

CASE REPORT

This 38 year old Negro male steward had been in good health until one year prior to his admission to the hospital, at which time he had noted the onset of progressive weight gain. Seven months before admission he began an attempt at weight reduction by the use of a "patent medicine" and dietary restrictions. During the next two months there was a weight loss of 35 pounds. In spite of abandonment of the attempts at weight reduction, his weight continued to decline until it reached a plateau three months before entry to the hospital. Examination by his private

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physician was reported to have revealed only a "slight anemia and low blood pressure." During the following month he experienced a loss of libido, decrease in body hair and increasingly easy fatigability. At this time his physician noted a few small nodes in the neck, for which the patient was given penicillin and sulfonamides. Shortly thereafter the development of pain in the joints, nasal stuffiness and dull headache led to the prescription of oral cortisone. The marked improvement in well-being led the patient to continue taking cortisone without further medical advice or supervision. Approximately four weeks after he began taking cortisone, polyuria and polydipsia became manifest. At this time, on the advice of his physician, he sought admission to the hospital.

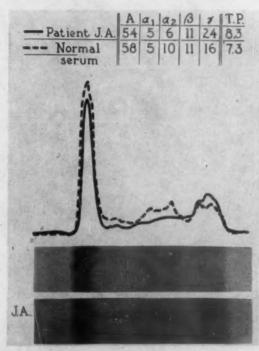


Fig. 1. Electrophoretic pattern of serum proteins compared with the normal.

Physical examination revealed a well developed, well nourished Negro male who appeared to be somewhat apprehensive. His blood pressure was 104/70 mm. of Hg; pulse, 76. His skin was a grayish hue, dry, thick and cool. The mucosal surfaces appeared to be pale. There was no chest hair and a noticeable absence of the outer one-third of the eyebrows. Axillary and pubic hair was sparse. In addition to several small, discrete, shotty inguinal nodes, there was a large, firm right epitrochlear node. Both testes were decreased in size, with a questionable decrease in consistency. The thyroid was not palpably enlarged. Examination of the visual fields revealed no abnormality.

Laboratory findings on admission included a hemoglobin level of 11.5 gm./100 ml.; hematocrit, 38%; white blood count, 6,900 per cubic millimeter, with 72% neu-



Fig. 2. Photomicrograph of lymph node section, showing granulomata without caseation (a) × 100.

trophils, 21% lymphocytes, 5% monocytes and 2% eosinophils. Total circulating eosinophils were 449 per cubic millimeter. The coagulation time was 7 minutes and the bleeding time, 3 minutes. Serum concentration of sodium was 146 mEq./L., of potassium 4.7 mEq./L., and of chlorides, 106 mEq./L. Serum calcium was 10.5 mg./100 c.c.; serum phosphorus, 4.1 mg./100 c.c. The carbon dioxide combining power was 27.9 mEq./L., alkaline phosphatase, 1.8 Bodansky units. Total serum cholesterol was 315 mg./100 c.c. An oral glucose tolerance test showed a fasting blood level of 70 mg./100 c.c., 125 mg./100 c.c. at one-half hour, 150 mg./100 c.c. at one hour, and 98 mg./100 c.c. at two hours. The bromsulfalein excretion test

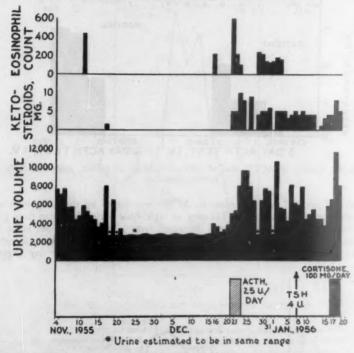


Fig. 3. Urine volume during first three months of study (see text). Asterisk denotes period when volume was not completely measured, but was estimated.

showed retention of 6.5% at 45 minutes. The serum protein level was 7.6 mg./100 c.c., with the albumin level 4.3 mg./100 c.c. and the globulin level, 3.3 mg./100 c.c. The thymol turbidity was 2.2 units. The serum electrophoretic pattern can be seen in figure 1. The spinal fluid protein was 96 mg.%; glucose, 65 mg.%; colloidal gold curve, normal; Kahn test, negative. Electroencephalograms showed a normal "waking" record. Study of sputum and excised lymph nodes by smear, culture and guinea pig inoculation failed to reveal tubercle bacilli. Lymph nodes and liver biopsy showed granulomatous inflammation consistent with sarcoidosis (figure 2). The skin reaction to PPD #1 was negative, but to PPD #2 was positive. Roentgenograms of chest, skull and long bones were interpreted as normal. Urine volumes can be seen in figure 3.

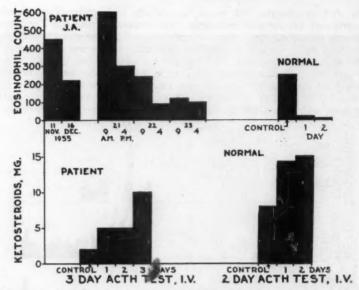


Fig. 4. Results of ACTH test of adrenal function in patient, compared with a normal response.

Adrenal cortical responsiveness to ACTH was tested by the daily intravenous administration of 25 units of ACTH over an eight-hour period for three days (figure 4). The circulating eosinophil level decreased from a value of 634 per cubic millimeter to a level of 88 per cubic millimeter, while the urinary 17-ketosteroid excretion increased from a basal level of 6 mg. per day to one of 10 mg. per day (figures 3

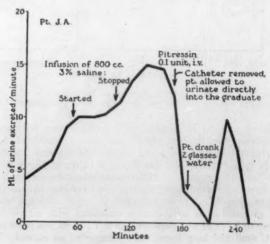


Fig. 5A. Hickey-Hare test before cortisone therapy.

and 4). The Robinson-Kepler-Power water test was "positive," with an overnight urine volume of 2,100 c.c., while the maximal one-hour output in the morning was only 200 c.c. A Hickey-Hare test (figure 5A) revealed diabetes insipidus. Repetition of this test while the patient was receiving 37.5 mg. of cortisone daily again was consistent with this diagnosis (figure 5B). It is of interest that the diuretic effect of hypertonic saline infusion was much more marked when the patient was receiving cortisone (figure 5B) than before (figure 5A). Urinary levels of 17-hydroxycorticoids after the ACTH test were 4.2 mg. and 6.9 mg./24 hours (figure 6), compared with a control level of 0.2 mg./24 hours.

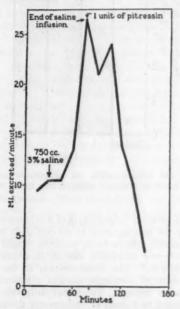


Fig. 5B. Hickey-Hare test after cortisone therapy.

The basal metabolic rate was minus 14 and minus 24 on two separate occasions. The radioactive iodine uptake was 10.2% at 24 hours (tracer dose was 24.7 μc of carrier-free iodine). Forty-eight hours after the administration of four units of thyrotropic hormone (Armour), the uptake had risen to 23.9% (figure 7). The urinary gonadotropin level was less than five rat units per 24-hour period, according to the method of Albert.

During the patient's first three days in the hospital the average urine volume was almost 8 L. per day (figure 3). During the following 15 days there was progressive but irregular decline in the volume of urine, reaching a level of 2 to 3 L. per day by the eighteenth hospital day. As may be seen in figure 3, the administration of the test dose of ACTH resulted in a sharp and transitory increase in the urine volume. Fluctuation in urine volume occurred in the subsequent eight days. The therapeutic administration of cortisone resulted in a marked increase in urine volume from the pretreatment level of 3 to 4 L. daily to a volume of 11 to 12 L. A slight further increase in urine volumes was noted following tri-iodothyronine administration.

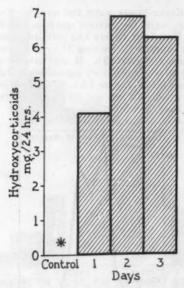


Fig. 6. Effect of ACTH administration on hydroxycorticoids excretion. Asterisk refers to control excretion hydroxycorticoids obtained two weeks after ACTH withdrawal, rather than before test.

Generalized weakness, striking fatigability and a marked intolerance to cold were complained of bitterly by the patient prior to the initiation of replacement therapy. During this period the systolic arterial blood pressure ranged from 80 to 90 mm. of Hg. While he was undergoing diagnostic studies, significant inguinal lymph node enlargement was first observed. The demonstration in the liver and in the epitrochlear and inguinal nodes of histologic changes consistent with sarcoidosis led to the initiation of cortisone therapy. The initial daily dose of cortisone was 300 mg., but was quickly reduced to a level of replacement therapy (37.5 mg.). Addition of tri-iodothyronine three weeks later resulted in improved skin and hair texture and tolerance for cold. One week later Pitressin Tannate in oil (0.4 c.c. daily) was added to the regimen, with a prompt decrease in the urine volume. Subsequently,

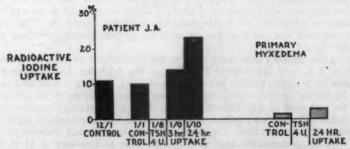


Fig. 7. Effect of administration of thyroid stimulating hormone on uptake of I¹⁸¹ by thyroid in patient, compared with response in patient with primary myxedema.

sublingual testosterone propionate was prescribed for treatment of impotence. On the combined regimen he felt completely well and was able to resume his occupation as a waiter.

Two months after discharge from the hospital there was recurrence of the polyuria, attributable to the failure to vary injection sites and to warm the Pitressin preparation prior to injection.

DISCUSSION

Granulomatous inflammation of the hypophysis is one of the infrequent causes of hypopituitarism. Tuberculosis, syphilis and nonspecific granulomatous lesions have all been reported as a cause of this syndrome.¹ Anterior pituitary insufficiency resulting from sarcoidosis of the pituitary has been reported by a number of workers.⁵ More frequent, however, is the syndrome of diabetes insipidus with sarcoidal involvement of the posterior pituitary and/or hypothalamus.³ 4

The coexistence of apparent diabetes insipidus and anterior pituitary insufficiency is a paradox, according to traditional endocrinologic concepts. Richter ⁹ demonstrated in experimental animals that diabetes insipidus does not occur in the absence of an intact anterior pituitary gland. Doxiades and Tiliakos, ¹⁰ Heinbecker et al. ¹¹ and Lipsett et al. ¹² have questioned the need of an intact anterior pituitary for the development of diabetes insipidus. Nevertheless, ^{11, 18} the bulk of the evidence suggests that, for permanent maximal diabetes insipidus, persistence of the pars anterior of the pituitary, or adequate substitution therapy is essential.

The data reported in this communication are in keeping with this concept. Only after investigation revealed that the patient had been taking moderately large doses of cortisone was the paradox of apparent combined anterior and posterior insufficiency resolved. The manifestations of diabetes insipidus disappeared with withdrawal of the cortisone. They reappeared with the administration of cortisone and with the test dose of ACTH administered for diagnostic purposes. The response to the latter test, the effect of thyroid-stimulating hormone administration on thyroid function and the low urinary gonadotropin level all demonstrated clearly the anterior pituitary insufficiency. Only when this was treated by the administration of cortisone and thyroid hormone was the diabetes insipidus "uncovered."

The presence of diabetes insipidus due to lack of endogenous antidiuretic hormone was demonstrated by a Hickey-Hare test (figure 5A). Instead of the usual decrease in urine volume following infusion of hypertonic saline, there was a diuresis. The response to Pitressin was prompt and dramatic. Comparison of figure 5A with 5B illustrates the effect of cortisone in improving the ability of a patient with adrenal cortical insufficiency to handle a water load.

The need for adrenocortical replacement for manifestations of diabetes inspidus of this patient was consistent with the observations of Ikkos, Luft and Olivercrona. These authors noted that patients hypophysectomized for metastatic carcinoma showed an initial polyuria for from two to six days after operation, and an interphase followed by a second polyuric phase. The second polyuric phase was maintained only when ACTH or cortisone was administered.

The diuretic effect of the anterior pituitary has been related, at least in part, to adrenal cortical and probably to thyroid function.^{11, 14-17} Adrenal cortical steroids have been shown to increase diuresis by increasing the solute load and

decreasing the osmolarity of the urine, necessitating a greater amount of water excretion and increasing glomerular filtration. The effect of thyroid hormone has also been related to increase in glomerular filtration and renal blood flow. Antidiuretic hormone, apparently elaborated by the supra-optic nuclei of the hypothalamus, is secreted along the pituitary stalk and stored in the posterior lobe of the pituitary, from whence it is released. Heinbecker and White ¹⁸ have shown that ablation of the posterior lobe will not result in diabetes insipidus if 15% of the cells of the supra-optic nuclei remain intact. According to these workers, these cells will produce sufficient antidiuretic hormone to prevent demonstrable diabetes insipidus. If these conclusions apply to such infiltrative disease as sarcoidosis, it may be assumed that both the pituitary gland and the hypothalamus are involved in our patients.

It is of interest that a sudden development of obesity preceded by six months all other evidence of disease. Thereafter, hypogonadism developed, followed by evidence of hypothyroidism. The tentative diagnosis was disease of the hypothalamus followed by pituitary involvement.

SUMMARY

A patient with sarcoidosis and anterior and posterior pituitary insufficiency is described. Clinical manifestations of diabetes insipidus appeared only upon the administration of cortisone.

SUMMARIO IN INTERLINGUA

Un steward negre de 38 annos de etate esseva hospitalisate con symptomas suggerente diabete insipide. Durante su sojorno al hospital, su production de urina decresceva ab un nivello initial de circa 8 L usque a 2 L, sin ulle medication. Le major gravamines de iste patiente esseva debilitate generalisate, fatigabilitate, e marcate non-toleration de frigido. Le investigation del function adreno-cortical, testicular, e thyroide confirmava le impression de insufficientia antero-pituitari. Biopsia de nodos lymphatic establiva sarcoidosis como etiologia probabile. Therapia substitutive con hydrocortisona e tri-iodothyronina causava le resurgentia de marcate grados de polyuria. Isto respondeva al tractamento con Pitressina in un prompte e dramatic maniera. Le coexistentia de apparente diabete insipide con insufficientia antero-pituitari es un paradoxo de que le explication se trova in le facto que le patiente habeva prendite cortisona ante su admission al hospital. Iste constatationes es congruente con le concepto traditional del relation inter le function antero-pituitari e diabete insipide.

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UNUSUAL REMISSION IN A CASE OF THROMBOTIC THROMBOCYTOPENIC PURPURA SYNDROME FOLLOWING FRESH BLOOD EXCHANGE **TRANSFUSIONS***

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EVER since its original description by Moschcowitz in 1925 as "an acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries" associated with a bleeding tendency, thrombotic thrombocytopenic

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purpura (TTP) has been reported with increasing frequency, especially in the last decade.^{2, 3, 4} With 78 cases reported in the available literature, and more known not to have been recorded, the disease is no longer considered to be unusually rare.

The anemia has been shown to be hemolytic, and the hemorrhagic tendency to be due to thrombocytopenia. However, the nature of the characteristic vascular thrombi has not been definitely elucidated. First attributed to erythrocytes,³ then thought to be composed of agglutinated platelets,⁵ the thrombi are now regarded largely as the result of endothelial lesions, conceived as the primary "prethrombotic" factor, with possible secondary platelet deposition.⁶ According to certain investigators, the vascular changes leading to formation of minute arteriolar and capillary aneurysms constitute the fundamental lesion.⁷

The syndrome is characterized by marked hemolytic anemia, thrombocytopenia, and signs of cerebral involvement which are at first transient. When all are present, these features make the diagnosis during life relatively easy.^{8, 9}

In most instances, early confirmatory histologic evidence of the diagnosis has not been available, except where splenectomy was performed. The thrombi of the small blood vessels are found primarily in the heart, muscle, brain (gray matter) and adrenal cortex. As a rule, skin and muscle biopsy has been negative during life, 10 although scattered lesions may occur. Cooper et al. 11 found typical thrombi of blood vessels in bone marrow sections, but this could not be confirmed by other authors. Involvement of splenic vessels has been noted in splenectomized patients, but splenic biopsy has been reported to be unreliable, and may be hazardous. 2

The disease usually has a sudden onset, with fever, prostration, the appearance of jaundice (usually mild), and purpura, mental confusion, and changing neurologic signs. Most patients have a very short, fatal course; rarely, there may be a more protracted course, and the full-blown picture may develop only after some time.

Thus the disease affects the blood vessels, the platelets and the red cells, by what appears to be, according to recent investigations, a common immunologic mechanism. When normal blood is injected into the patient's circulation, survival of both red cells and platelets is considerably shorter than normal, indicating extrinsic hemolytic mechanisms. However, no definite immunologic agents have been detected. A careful search for abnormal antibodies of both the red cell and the platelet type has usually proved to be negative. The Coombs' test has been characteristically negative in the overwhelming majority of cases. To explain this, it has been postulated that the elusive antibody is not associated with the globulin fraction, or that it does not appear in the cell coating.

The etiology remains unknown. A number of possible provoking factors have been noted. The probability of an unusual allergic type of response has been considered, since this syndrome has been seen following smallpox vaccination, influenza or tetanus immunization, drug sensitivity, etc. The disease may be related to the "family" of collagen diseases. Association with lupus erythematosus has been reported. The morphology of the thrombotic lesions varies according to the stage of the disease.

No effective treatment is available. In very occasional instances the disease

enters a phase of spontaneous or possibly induced remission, which may last as long as two or three years. In one patient, splenectomy was followed by a long remission.¹⁴ However, in the majority, splenectomy was unsuccessful, perhaps because there has been little opportunity to attempt this procedure early in the disease, before irreversible damage has been done. Stress has been laid in more recently reported cases of thrombotic thrombocytopenic purpura on the fact that ACTH and cortisone are ineffective.

We have observed a case that fits the clinical criteria of TTP mentioned above, and that is reported because of the unusual clinical response following exchange transfusions using fresh whole blood. This procedure was chosen because of the patient's extremely poor condition. The risk of splenectomy seemed too great. The case brought to mind a chance observation made some years ago by one of us (M. R.) in another patient with the same disease. That patient was bleeding profusely because of thrombocytopenia. Repeated fresh blood transfusions were given to stop hemorrhage, following which a temporary period of improvement was noted. This particular patient was not followed by us, but in retrospect his course was viewed as showing temporary improvement following a partial exchange transfusion.

CASE REPORT

An 11 year old white girl was admitted to another hospital on February 20, 1958, with a six-day history of sudden onset of fever, nausea and vomiting, and difficulty in speech. The next day there was some mental confusion, which changed in character from time to time; mild jaundice and small petechiae over the legs and forearms appeared on the third day.

Prior to the present illness the patient had been in good health. There was no past or family history of jaundice or anemia. Physical examination showed a well developed 11 year old girl who manifested transitory periods of stupor. According to the nurse's report, the patient at times appeared to be quite normal, only to lapse into more or less marked stupor and states of mental confusion. The Babinski reflexes were reported to change from negative to moderately positive on different days. The skin and sclerae were icteric. The urine became dark red, and numerous red cells were found in the sediment.

When the patient cas seen on March 1, 1958, her hemoglobin was 4.7 gm.%; hematocrit, 14; white blood cells, 14,200, with 66% segmented neutrophils, 5% non-segmented neutrophils, 25% lymphocytes and 4% monocytes. The blood smear revealed about 30% of the red cells to be large polychromatophilic cells, and about the same number to be small spherocytes, giving a biphasic character to the red cell population. In addition, the red cells showed numerous instances of fragmentation. The reticulocyte count was 34%. These findings indicated increased hemolysis. There was other evidence of the hemolytic process. The red cell fragility was increased, the hemolysis starting at 0.52% sodium chloride, and being completed at 0.32% sodium chloride. (The red cell fragility of both parents was normal.) The icteric index was 25. The serum bilirubin was 4.5 mg.%. The platelet count was between 80,000 and 20,000 per cubic millimeter.

Bone marrow aspiration of the iliac crest, performed on March 2, 1958, showed cellular marrow (total nucleated cell count of 135,000 per cubic millimeter). It also showed marked erythroid hyperplasia, with nests of erythroblasts and normoblasts crowding out other marrow elements. There was no evidence of arrest of maturation in the erythroid or myeloid elements. The myeloid series showed normal cell distribution, but they were reduced in their relative percentage count. The

megakaryocytes were markedly reduced in number, and showed evidence of inadequate platelet formation.

The blood chlorides, sodium, potassium and CO₂ combining capacity were within normal limits. Coombs' test (direct, indirect and acidified) was negative on repeated examination. The acid hemolysis test (Ham's test) was negative.

On March 2, 1958, the stuporous states were noted with increasing frequency. On the morning of March 4, 1958, 12 days after the onset of the illness, the child lapsed into deep, persistent coma. The temperature, moderately elevated at the beginning (102° F.), became normal after a few days.

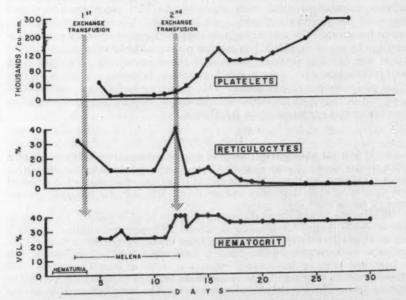


Fig. 1. Reticulocyte and platelet counts following exchange transfusion. Decrease in reticulocytes and increase in platelets are especially marked following second exchange transfusion. Failure of platelets to rise after the first exchange transfusion might have been due, in part, to gastrointestinal bleeding and previous frequent simple transfusions with stored blood.

The initial therapy consisted of intravenous infusions of glucose and saline, whole blood transfusions, ACTH in increasing doses (up to 40 units four times a day), and antibiotics (penicillin and tetracycline). When after a few days the patient gave the impression of having improved in clinical appearance, ACTH was changed to prednisone, given orally in doses of 30 mg. a day. However, she soon lapsed into stupor, and ACTH was resumed in the same dosage as before, but without effect. When, later, the diagnosis of thrombotic thrombocytopenic purpura was made, this short period of apparent improvement was regarded not as a result of ACTH, but as a part of the changing clinical and hematologic picture, characteristic of the disease.

The working diagnosis of thrombotic thrombocytopenic purpura was made on the basis of the characteristic signs: hemolytic anemia, thrombocytopenia, and changing cerebral manifestations. The possibility of hereditary spherocytic hemolytic anemia was ruled out by history, absence of splenomegaly at the beginning, and the fact that the red cell fragility of both parents was found to be normal. The possibility of paroxysmal nocturnal hemoglobinuria was ruled out by the negative acid hemolysis test. The possibility of infectious mononucleosis was considered in the beginning, but at no time were atypical hyphocytes or lymphadenopathy found that could be suggestive of this diagnosis. Leterophil test was negative. Repeated blood and bone marrow preparations in a search for L.E. cells gave negative results.

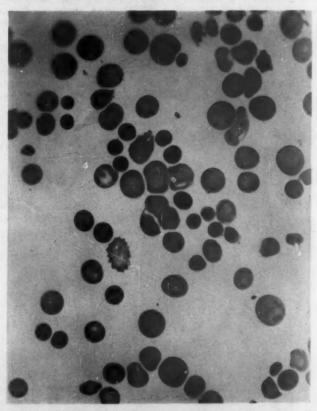


Fig. 2. Peripheral blood smear before the exchange transfusion, showing biphasic red cell population (small cells representing spherocytes, large cells, reticulocytes); fragmentation of red cells was very marked.

On March 4 the patient was transferred to the Cedars of Lebanon Hospital. On admission she was comatose and icteric. Her breath was foul, and saliva drooled from her mouth. The sclerae were jaundiced, the pupils dilated and fixed. Her eyes wandered aimlessly. Funduscopic examination revealed a hemorrhage at the lateral margin of the head of the right optic nerve. There was no gag reflex. The breathing was shallow, irregular and labored. There were decreased breath sounds over the right upper and middle lobes. However, there were no abnormal findings in the chest x-ray. Blood pressure was 110/70 mm. of Hg. Heart tones were

good, with a regular rate. The liver edge was 2 cm. below the costal margin. The spleen was not palpable. There were bilateral positive Babinski reflexes and a right hemiparesis. Laboratory findings (prior to her admission, the patient had received 3,600 c.c. of whole blood): hemoglobin 9.2 gm.%; hematocrit, 26; white blood cells, 15,200; platelet count, 48,000; serum bilirubin, 5 mg.%; prothrombin time, 80%; cephalin flocculation, 3 plus; urine, 4 plus albumin and numerous red cells.

The patient was given large doses of hydrocortisone (150 mg, every six hours in intravenous infusions), in addition to ACTH (40 mg, four times daily); this was done because of the possibility that ACTH alone might not be effective.*

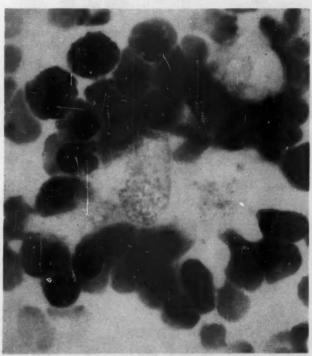


Fig. 3. Photomicrograph of a bone marrow smear before transfusion, showing erythronormoblastic proliferation.

The patient was given penicillin and streptomycin, and tetracycline intravenously. She was also given intravenous glucose and saline, with added potassium chloride (40 mEq.) and 400 mg. of ascorbic acid. Testosterone propionate was given from March 4 to March 6, 15 mg. daily in intramuscular injections. No improvement was seen.

On March 6 the patient received her first blood exchange transfusion—2,000 c.c. of fresh whole blood, from four to 12 hours after it was taken from donors. The next day she reacted more strongly to stimuli. The following day she emerged somewhat from the stuporous state. She opened her eyes and seemed to react to light stimuli. She could not understand when spoken to, nor was she able to take

^{*} The adrenal cortex may be involved in thrombotic thrombocytopenic purpura.

food orally. This improvement was of short duration. On March 10 she was found in a state of convulsions and apnea, and was placed in a Drinker respirator.

The laboratory findings following the first exchange transfusion are presented in figure 1. There was a drop in reticulocyte count from 31% before to 18% the next day after, with the lowest count (13%) on March 10. One remarkable finding following the first exchange transfusion was the absence of blood in the urine. The urine became clear after this exchange transfusion for the first time, and remained so throughout the patient's hospital stay.

The evaluation of the red cell count as a measure of the degree of hemolysis was more difficult. On March 10 the patient began to have profuse gastrointestinal bleeding. The possibility that the high doses of hydrocortisone and ACTH might have been a contributing factor to this bleeding was considered. This therapy was therefore gradually discontinued.

With the onset of this clinical relapse there was evidence of increased hemolysis: on March 12 the reticulocyte count rose to 39%, spherocytosis increased, and the serum bilirubin, which initially had fallen from 5 mg.% to 1.2 mg.%, was again high.

On March 12 a second exchange transfusion, more nearly complete than the first one, was given; 3,000 c.c. of whole blood, six hours old and stored in siliconized containers, were used. A dramatic improvement, both clinical and hematologic, was seen after this procedure (figure 1). The reticulocyte count fell and at the same time the platelet count showed a gradual rise. The day after the exchange transfusion, reticulocytes decreased sharply (from 39% to 8%); on March 17 the count was 3%, and fell to 0.7% on March 21. However, before the patient's discharge from the hospital, and during the following three months (up to the time of writing), the reticulocyte count rose somewhat, and ranged between 3% and 5%. The platelet count showed a parallel increase: the day after the transfusion it was 32,000 per cubic millimeter, rose to 100,000 on March 17, and attained normal levels (267,000) on March 28. Ever since then it has remained within normal range (between 260,000 and 280,000). Serum bilirubin was 0.44 mg.% on April 2, reflecting the subsiding hemolytic disease. The red cell count remained at normal levels (hemoglobin ranged between 12.3 gm. and 13.1 gm., and hematocrit between 36% and 38% red cell volume). The patient was given no further transfusions.

At the same time there was rapid clinical improvement. The patient regained complete consciousness the day after the second exchange transfusion. She soon started to eat and to respond to her environment. Her abnormal neurologic signs gradually disappeared. Babinski reflexes became negative.

The patient was discharged on April 18 with normal neurologic findings, including complete return of speech and only slight amnesia. The blood count was essentially normal at the time of writing (15 months after discharge from the hospital), except for a slight reticulocytosis (up to 5%). Before discharge from the hospital a skin biopsy and a bone marrow aspiration were performed. The skin was normal. The bone marrow aspiration showed a normal M.E. ratio consistent with the blood studies, which showed a subsided hemolytic process, and normal megakaryocytic activity in accordance with the normal platelet count. However, there was an increased number of reticulum-like cells which had not been seen on the first aspiration.

DISCUSSION

This case is reported because of the unusual therapeutic response to exchange transfusions with fresh blood, a hitherto unreported procedure in thrombotic thrombocytopenic purpura.

The working diagnosis of TTP was made on the basis of the characteristic

triad of hemolysis, thrombocytopenia and changing cerebral manifestations. The patient appeared to be mentally confused; she had stuporous states alternating with more lucid intervals, and a transient hemiparesis with 1 plus to 3 plus positive Babinski reflexes. Hematologic studies confirmed a hemolytic anemia and thrombocytopenia: high reticulocyte count, elevated serum bilirubin, increased red cell fragility, low platelet count, and characteristic bone marrow picture, with erythroid hyperplasia and megakaryocytes showing failure of platelet formation.

Other findings consistent with the diagnosis were: (1) sudden febrile onset; (2) negative Coombs' test; (3) lack of response to cortisone and ACTH; (4) urinary finding of albuminuria and red cells. Like most of the reported cases of thrombotic thrombocytopenic purpura, there was no lymphadenopathy, the tourniquet test was negative in spite of marked thrombocytopenia, and the

icterus was also mild in view of the severity of the hemolytic process.

The definitive diagnosis of thrombotic thrombocytopenic purpura consists in demonstrating the characteristic vascular lesions in tissue sections. When the diagnosis is made during life, and when histologic evidence is unavailable (a negative skin biopsy does not rule out the diagnosis), it may be best to term the condition "thrombotic thrombocytopenic purpura syndrome." In this case, certain disease entities that may occasionally be associated with a somewhat similar picture were considered, then ruled out:

1. Paroxysmal nocturnal hemoglobinuria, which may occasionally be associated with intravascular thrombosis, adding the possibility of cerebral involvement to signs of hemolysis and thrombocytopenia, was ruled out by the negative

history and negative acid hemolysis test.

2. At the beginning, infectious mononucleosis was also considered as a possibility, but at no time were atypical lymphocytes seen in the blood smear. Lymphadenopathy was not present, and the heterophil test was negative. Occasionally, infectious mononucleosis may be associated with thrombocytopenia or hemolytic anemia, and bizarre neurologic manifestations may occasionally occur in this disease. However, the changing character of the neurologic manifestations has not been described as a typical feature of infectious mononucleosis. We have found no case in the available literature of infectious mononucleosis showing the simultaneous occurrence of thrombocytopenia, hemolytic anemia and neurologic manifestations.

Combinations of acquired acute hemolytic anemia and idiopathic thrombocytopenic purpura have been described in syndromes given different names (Fisher-Evans syndrome, ¹⁶ etc.), with occasional renal involvement.¹⁷ However, no cerebral manifestations have been described in these syndromes, and Coombs'

test was usually positive in these cases.

Characteristically, in our patient the direct and indirect Coombs' test has been repeatedly negative. To our knowledge, with the exception of two instances, this test has been reported to be negative in all cases of thrombotic thrombocytopenic purpura recorded in the literature. On the other hand, Coombs' test has as a rule been positive in other cases of acquired hemolytic anemia.

Also characteristic is the lack of response to ACTH and cortisone. This is the experience reported in the literature in thrombotic thrombocytopenic purpura. The unusual and dramatic improvement that followed exchange transfusions was the most striking aspect of this case. The following observations are worthy of note:

1. While clinical and some hematologic improvement was found after each of the two exchange transfusions, a more pronounced effect was observed after the second exchange transfusion, which was also more nearly complete than the first one.

2. After the second exchange transfusion there was an immediate parallel improvement in the clinical and hematologic condition. Dramatic improvement was observed almost simultaneously in the clinical appearance and in the hemolytic and thrombocytopenic manifestations.

3. Practically all of the symptoms and signs of the disease proved to be reversible. The patient came out of deep coma, and was taken out of the respirator; she was able to swallow, responded to her environment, and regained speech and memory. At the same time, the hemolysis subsided, the platelet count returned to normal, and the hemorrhagic tendency was corrected.

The mechanism of the benefits of the exchange transfusions is not clear. One may speculate that circulating antibodies were removed, while formation of new antibodies was inhibited by the previously administered high dosages of cortisone and ACTH. Also, for a short time the patient had been given some test sterone, and its role is difficult to ascertain. It is possible that the therapeutic effect is attributable to the combined result of treatment.

In discussing any therapeutic effect in thrombotic thrombocytopenic purpura, one should be mindful of the fact that chronic forms of the disease, although very rare, have been described. In this connection, the case reported by Gardner et al. seems to be of interest. The authors reported a patient who recovered from acute hemolytic anemia at eight years of age, and died 18 years later with findings typical of TTP. The possibility of a long remission in this disease was discussed by the authors.

SUMMARY

A case of thrombotic thrombocytopenic purpura syndrome is reported in an 11 year old girl with acute hemolytic anemia, thrombocytopenia and changing neurologic manifestations; these were at first transitory, but later led to hemiparesis and deep coma. Other findings consistent with the diagnosis of thrombotic thrombocytopenic purpura included sudden febrile onset, hematuria, a negative Coombs' test, and lack of response to cortisone and ACTH. No histologic evidence of the diagnosis was found in one skin biopsy taken after improvement was evident. The differential diagnosis (paroxysmal nocturnal hemoglobinuria, hereditary spherocytic hemolytic anemia, infectious mononucleosis) was discussed.

Exchange transfusions with fresh blood were followed by an immediate and dramatic improvement. The patient came out of deep coma and was taken out of the respirator; she was able to swallow, responded to environment, and regained speech and memory. At the same time, hemolysis subsided and the platelet count returned to normal. At this time (15 months after discharge

from the hospital), the patient appears to be normal, both clinically and hematologically.

ADDENDUM

Patient led a normal life, including full school attendance until August, 1959. She remained asymptomatic during this 16-month interval, except for a two months' period of tonsillitis in October, 1958. During this time, both tonsils were huge but they became smaller slowly and spontaneously. At the end of August, 1959, for the first time an anemia (hemoglobin 11 gm.) was found, and it progressed to a hemoglobin of 7.5 gm. at the end of September.

During the latter period she had daily temperature elevations of 103° F. orally. Generalized lymphadenopathy was noted, most marked in the posterior auricular nodes. She had nausea and vomiting and a seven pound loss of weight. Her urine showed numerous pus cells and red cells, and the urine culture revealed enterococci, E. coli, and Staphylococcus aureus, coagulase positive. At this time, L.E. cells were found in the blood on repeated examinations. Serum protein electrophoretic studies showed a gamma globulin of 3.7 gm.%.

Patient was hospitalized September 22, 1959, and is now being further investigated.

As mentioned above, the occurrence of L.E. cells in the course of thrombotic thrombocytopenic purpura and its relationship to lupus erythematosus has been discussed in the literature.¹²

The patient is probably entering a relapse after a remarkably long remission of 16 months following exchange transfusions with fresh blood.

ACKNOWLEDGMENT

We acknowledge with thanks the valuable collaboration of Dr. J. Frieden, Dr. M. Goodwin and Dr. M. Harris, and the members of the house and nursing staffs.

SUMMARIO IN INTERLINGUA

Es reportate le occurrentia inusual de un remission dramatic in un caso del syndrome de acute purpura thrombotic thrombocytopenic (PTT). Iste remission esseva observate post repetite transfusiones de excambio con sanguine fresc (duo)—un mesura que non ha previemente essite reportate in casos de iste disordine.

Il se tracta del caso de un puera de racia blanc de 11 annos de etate. Le historia clinic habeva comenciate in acute febrilitate con bizarre manifestationes neurologic. Initialmente istos habeva essite transitori e de character variabile, sed illos se disveloppava plus tarde in un profunde coma. Esseva constatate sever hemolytic anemia spherocytic e marcate grados de thrombocytopenia. A parte iste triade diagnostic de anemia hemolytic, thrombocytopenia, e variabile manifestationes menual ric, hematuria esseva presente e le test de Coombs esseva characteristicamente negative. Therapia a ACTH e cortisona remaneva sin effecto—un facto a expectar in PTT. Tamen, nulle confirmation histologic del diagnose esseva disponibile, e le termino "syndrome de PTT" esseva preferite a "morbo de PTT". Le curso del patiente sequeva un deterioration rapide. Le hemoglobina descendeva a 5 g, e repetite transfusiones de sanguine de banca esseva administrate sin que le curso del morbo se monstrava influentiate.

A causa de un observation accidental (facite plure annos retro sed nunc rememorate), transfusiones de excambio con sanguine fresc esseva effectuate. Duo tales esseva essayate e resultava in un melioration inusual. Post le prime (incomplete) transfusion de excambio, le patiente surgeva ex le coma, le urina se clarificava de hemorrhagia, e le intensitate del hemolyse pareva diminuer. Tamen, brevemente plus tarde, le thrombocytopenia e le hemolyse redeveniva marcate. Un secunde e plus tosto complete transfusion de excambio esseva usate, e un remission ancora plus dramatic sequeva, tanto clinica- como etiam hematologicamente. Le patiente deveniva mentalmente vivace e recomenciava parlar e mangiar etc. Al mesme tem-

pore le hemolyse subsideva. Le reticulocytos decresceva ab 30 a 0,7 pro cento, e le thrombocytos montava in 10 dies ab 10.000 a 185.000. Le hemoglobina se manteneva a nivellos normal, e nulle transfusiones additional esseva requirite. Durante 16 menses le patiente pareva clinicamente e hematologicamente normal. Le sol exception esseva le presentia sporadic de leve grados de reticulocytosis (3 a 5 pro cento). Illa duceva un vita normal, incluse le assister al classes sin interruption. Durante le dece-septime mense, un sever anemia se disveloppava con febre e lymphadenopathia generalisate. Cellulas L.E. esseva trovate repetitemente in le sanguine. Le patiente esseva readmittite al hospital verso le fin de septembre 1959. Le natura de iste recidiva es sub investigation.

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THE SYNDROME OF HYPONATREMIA AND RENAL SODIUM LOSS PROBABLY RESULTING FROM INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE *

By H. J. ROBERTS, M.D., West Palm Beach, Florida

THIS paper reports a patient with a bronchogenic carcinoma who developed profound hyponatremia and hypochloremia in association with considerable loss of both sodium and chloride in the urine. Clinically he was found to have normal renal and adrenal function and at autopsy the kidneys and the adrenals showed no significant pathologic change.

Two earlier instances of this particular syndrome were included in the report by Schwartz et al. in 1957.1 It was the opinion of these investigators that this unusual electrolyte derangement could best be explained by a sustained and inappropriate secretion of antidiuretic hormone, and that this disorder was a consequence of the resultant expansion of the body fluid volume. The patient herein reported seems to duplicate their two patients in most respects.

CASE REPORT

A 56 year old yacht captain was first seen in consultation with the chief complaint of syncopal-like episodes of several days' duration. He had recently been treated for a presumed respiratory tract infection with various antibiotics and nonspecific medication. A chest film revealed a definite mass in the left hilar area, consistent with a bronchogenic carcinoma. The patient initially declined to enter the hospital for further observation. During this time he was given supportive therapy and was urged to stop smoking. Three sputum examinations studied by both smear and culture for acid-fast organisms were negative.

A history was obtained of the patient's having had "some trouble with the bowels" for approximately the last two months. At that time he had had an upper gastrointestinal x-ray series performed which revealed an active duodenal ulcer with some esophagitis and considerable edema in the antral area. The patient also gave a history of a duodenal ulcer in 1941. In the last several months there had been some associated decrease in his appetite, and a weight loss amounting to 10 pounds. He also complained of increasingly uncomfortable pains in the hips and limbs. In view of the absence of metastases by x-ray, this was interpreted as a probable osteoarthropathy related to the pulmonary and mediastinal pathology (see Discussion).

When the patient was first seen he had had persistent nausea and some vomiting of several days' duration. In spite of parenteral atropine in small amounts, he was unable to retain any nourishment. He was accordingly admitted to St. Mary's Hospital on March 7, 1958 with the diagnosis of a probable pyloroduodenal obstruction secondary to his active duodenal ulcer.

The patient's past history was significant in the following respects: he had always been an excessively heavy smoker, smoking at least one and one-half packages of cigarettes daily; he had in the past consumed large amounts of alcohol, but had done no drinking for nine years.

The physical examination shortly after admission to the hospital revealed a well developed and fairly well nourished white male, complaining of considerable nausea

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and appearing to be chronically ill. There was no evidence of marked dehydration. The other significant findings included moderate emphysema bilaterally, with some scoliosis, and suppressed breath sounds over both lower lung fields. The heart was not remarkable; no enlargement of the liver or spleen could be demonstrated by palpation or percussion. There was no succussion splash in the abdomen. The prostate was slightly enlarged. No adenopathy, clubbing of the fingers, or pigmentation was observed.

The patient was initially treated for his upper gastrointestinal obstruction with a regimen of modified feeding and aspiration, parenteral atropine in small doses, abstinence from smoking, and small amounts of antacids, along with parenteral fluids, electrolytes and vitamins. The obstruction was relieved very satisfactorily within a period of several days, only 20 ml. of residual gastric secretion being aspirated by the morning of the third hospital day. He had very few symptoms referable to the gastrointestinal tract throughout the remainder of his hospitalization.

It was noted on March 8, 1958, that the patient's blood sodium was 100 mEq./L. and that his serum chloride was 82 mEq./L. These low levels seemed quite inconsistent with the small amounts of vomitus that had been produced. The remainder of his blood chemical tests, including nonprotein nitrogen, serum potassium, serum amylase, total protein and A/G ratio were within normal limits, as were the urinalysis and serologic test for syphilis. The urine concentrations on random specimens ranged from 1.006 to 1.014. No free hydrochloric acid or occult blood was noted in the gastric aspirates. The stools were negative for blood and parasites. A bromsulphalein test revealed 11% retention of the dye at 45 minutes.

The serum electrolytes were checked again on several occasions (table 1). The highest serum sodium level prior to therapy was 121.5 mEq./L.; the highest serum chloride, 81.3 mEq./L. The potassium averaged 4.3 mEq./L. The serum CO₂ was 25.3 mEq./L. The urine output was quite satisfactory, averaging 2,000 to 2,500 ml. per day. In spite of the profound decrease in the serum sodium and chloride, the patient continued to excrete fairly large amounts of both chloride and sodium in his urine, with the urinary chlorides ranging from 87.2 to 90.2 mEq./L., and the urinary sodium averaging 111 mEq./L. The serum phosphorus and calcium were within normal limits. The creatinine was 0.6 mg.%. A fasting blood sugar was 108 mg.%. Two total eosinophil determinations were performed in the fasting state, the first being 711 per cubic millimeter, and the second, 688 per cubic millimeter. After his obstruction had abated and the activity of his ulcer had been controlled to some extent, corticotropin was administered intravenously (25 units over eight hours); the ensuing percentage drop was 32%.

The patient was regarded as having a probable bronchogenic carcinoma as the basis of his mediastinal mass, with probable invasion of the mediastinum to account for his syncopal-like episodes (see Discussion). He was bronchoscoped, and a left scalene node biopsy was performed in an attempt to ascertain positively the presence of metastases.* Malignant cells could not be found by the pathologist. During the course of this procedure the patient was found to be extremely sensitive to even small doses of hypnotics and morphine.

In view of the necessity for considering surgery in order to offer this man a possible hope for curative surgical resection of his neoplasm, it was necessary first to explain and to treat his electrolyte disturbance. The possibility of adrenal insufficiency was raised on the basis of metastases from his bronchogenic carcinoma—in part because of the low serum sodium, the low serum chloride, the marked sensitivity to narcotics, and the borderline eosinophil response to corticotropin stimulation. This diagnosis did not appear to be too likely, however, in view of the absent pigmentation, the normal blood pressure, the normal pubic and axillary hair, and the

^{*} Performed by Dr. Ivan Schmidt.

absence of dehydration. It was further ruled out by several studies of the urinary steroids. These revealed a per diem excretion of 13.8 mg. 17-ketosteroids (normal, 6 to 22 mg. for 24 hours), and 10.2 mg. 17-hydroxycorticoids (normal, 3.3 to 9.6 mg. for 24 hours).

The next consideration raised was that of a possible salt-losing nephritis. The patient gave no history or evidence of any previous urinary difficulty or albuminuria.

TABLE 1 Significant Laboratory Data

| March | NPN mg. % | Creatinine % | Serum Na mEq./L. | Serum Cl mEq./L. | CO ₃ mEq./L. | mEq./L. | Urine C mEq./L |
|----------------|--------------|--------------|---------------------|---------------------|----------------------------|---------|-------------------|
| 8 9 | 28 | | 100 122 | 82.3 78.4 | | 4.31 | |
| 13 14 15 | | | 118 125 | 81.3 78.4 | | | 87.2 |
| 17 20 | 21 | 0.6 | 121.5 121.5 | 85.3 81.3 | 25.3 | 3.90 | 01.2 |
| 21 | | | | | | | 90.2 |
| 22 | | | | | | | |
| 26 29 | | | 128.5 127.2 | 93.1 92.1 | 25.6 | 5.75 | - |

TABLE 1-(Continued)

| March | Urine Na mEq./L. | Eosinophils (total) | Other Significant Studies |
|----------------------|---------------------|---------------------|--|
| 8 9 | | | T.P.—6.0 gm.% |
| 12 | | | A/G. ratio—3.6 |
| 13 | | 802 | 1000 115000 |
| 14 15 17 20 | 102 | | |
| 17 | | | and the same of th |
| 20 | | | P—2.0 mEq./L. Ca—4.75 mEq./L. |
| 21 | 111 | 688 | |
| 22 | | 466 (after ACTH) | 17-ketosteroids, 13.8 mg./24 hrs. 17-hydroxycorticoids, 10.2 mg./24 hrs |
| 26 | | A CHARLES | 17-nymoxycorticolus, 10.2 mg./24 ms |
| 29 | | 1000 | |

Repeat nonprotein nitrogen examinations were within normal limits, averaging 21 mg.%. The creatinine was 0.50 mg.%. Several attempts were made to perform renal function tests, but were not satisfactory because of technical difficulties.

An attempt was made to ascertain the patient's response to intravenous sodium chloride and forced oral salt feeding. He was accordingly placed on doses of oral sodium chloride, starting at 3 gm. daily and gradually increasing to 9 gm. daily, in addition to the liberal use of salt in his food. He was also given a total of 500 ml. of 5% sodium chloride over several days. This forcing of salt made very little difference in his blood chemical tests, the highest levels recorded being 128 mEq./L.

for sodium and 93 mEq./L. for chloride. There was no significant weight gain during this period of salt loading.

Both corticotropin and parenteral cortisone acetate were given, primarily in an attempt to prepare the patient for a possible adrenal crisis associated with his anticipated surgery. There was likewise no significant change in his serum sodium or chloride; neither was there any reduction in the high concentration of urinary sodium and chlorides. Studies of his electrolyte response to intravenous alcohol and dehydration were planned, along with measurements of his extracellular fluid volume. The desire of both the patient and the thoracic surgeon to proceed with surgery at the earliest opportunity, however, precluded such observations.

The patient was subjected to an exploratory thoracotomy on March 24, 1958. At that time a large tumor mass was found arising from the left main stem bronchus and extending to the mediastinum, with invasion of the arch of the aorta and the region of the superior pulmonary vein. A biopsy was taken which proved the mass to be a bronchogenic carcinoma of the anaplastic type. No further surgery was attempted. The patient appeared to fare quite well for a period of several days. He was able to eat, and ingested 6 gm. of salt daily. He also received cortisone acetate, 25 mg. intramuscularly every 12 hours. On the third postoperative day, however, he evidenced considerable bleeding in the pleural cavity, associated with a profound drop in his hemoglobin and hematocrit. In spite of large amounts of blood and the use of many hemostatic substances, his condition rapidly deteriorated and he died on March 30, 1958.

A postmortem examination * confirmed the presence of the bronchogenic carcinoma, with extensive metastases to the mediastinum and the liver. The adrenal glands were carefully examined, as were the kidneys, the hypothalamic region and the pituitary. No overt metastases or significant gross or microscopic pathologic changes could be demonstrated in any of these areas. A healing duodenal ulcer was noted.

It was the author's final opinion that the patient's profoundly low sodium and chloride disorder represented a unique manifestation of his bronchogenic carcinoma, with an inappropriate handling of these substances by the kidneys, similar to that of the two patients described by Schwartz et al. A personal communication from Dr. William Schwartz expressed the same opinion.

DISCUSSION

The clinical crux of this particular problem resides in the finding of a progressive hyponatremia and hypochloremia, with a paradoxic excessive urinary excretion of sodium and chloride in the presence of normal function of both the kidneys and the adrenal glands. As was indicated in the case report, the possibilities of a symptomatic adrenal insufficiency secondary to metastases of the bronchogenic carcinoma and a salt-losing nephritis were both initially entertained, but could not be corroborated by clinical, laboratory and pathologic study. The other unusual aspect of this particular syndrome relates to the fact that neither clinical evidence of dehydration nor contraction of the body fluid volume became manifest as the depletion of the sodium and hypotonicity of the plasma progressed, notwithstanding the persistently hypertonic urine as compared with the plasma.

Schwartz and his colleagues have postulated that in their patients the underlying bronchogenic carcinoma induced a sustained and inappropriate secre-

^{*} Performed by Dr. Jackson L. Thatcher.

tion of antidiuretic hormone. They point out that the hypertonicity of the urine in the presence of a normal glomerular filtration rate poses clear-cut evidence for the presence of the antidiuretic hormone influence. It was further felt that this syndrome was related to the expansion of the body fluid volume.

The actual stimulus to the release of antidiuretic hormone in this instance is not clear. One might postulate the following possibilities, or any combination thereof: (1) a vagal and neurogenic basis, related to the invasion of nerves in the mediastinum; (2) a cerebral factor, possibly similar to the salt loss occasionally noted in brain disease; (3) hepatic disease, such as may have been partly the basis in this case (the patient's previous drinking, the elevated bromsulphalein retention, and the presence of metastases), particularly when considered in light of the fact that the liver inactivates antidiuretic hormone; and (4) the secretion or release of some humoral agent. With reference to the latter, one is reminded of the ability of large tumors in the mediastinum or retroperitoneal areas to produce either insulin or insulin-like substances,² and of the Zollinger-Ellison syndrome.³ The presence of an active duodenal ulcer in this patient and in one of the patients observed by Schwartz and his colleagues is of some interest in this regard.

Some current concepts pertaining to the basic tubular events in the dilution and concentration of urine in the mammalian kidney merit brief mention. Berliner and his colleagues cite the following pertinent features:

- 1. The glomerular filtrate is iso-osmotic with the plasma.
- There is active reabsorption of sodium and chloride in the water-permeable proximal convoluted segment, resulting in a reduction in volume but not in the osmotic pressure of the tubular fluid.
- 3. There is active sodium transport out of the water-impermeable loop of Henle, creating dilution of the tubular contents and hypertonicity of the medullary interstitial fluid. The permeability to water of the loop epithelium is apparently not modified by antidiuretic hormone.
- 4. Under the influence of sufficient antidiuretic hormone, the distal convoluted tubule and collecting ducts become relatively water-permeable. This permits the egress of water into the cortical interstitial fluid, and a dissipation of the hypotonicity of the fluid entering the distal convoluted tubule.

It is pointed out that, in the change from water diuresis to antidiuresis, the removal of water from the urine beyond the distal convoluted tubule is much more fundamental to the production of a hypertonic urine than is the addition of solutes or the medullary blood flow.

The diminished urine flow caused by antidiuretic hormone activity therefore stems from the increase in the tubular reabsorption of water and an associated inhibition of the reabsorption of sodium chloride. In many species there is also an enhanced excretion of sodium. In basic studies performed by Leaf and his associates, it was clearly shown that the increased excretion of sodium and chloride produced by Pitressin was the result of water retention and *not* a direct effect of this substance.⁵ Such a phenomenon probably represents a homeostatic response to overexpansion of the fluid volume.

The above cited investigators were able to produce a response very similar

to that observed in these patients with bronchogenic carcinoma—viz., renal sodium loss and hyponatremia—by the continuous administration of Pitressin and sufficient water, the osmolality of which was less than that of the urine.⁵ They were also able to show that the sodium loss and hyponatremia could be prevented in large measure by the restriction of fluids. The renal sodium loss stemming from such "inappropriate" antidiuretic hormone secretion probably can be further related to an increased glomerular filtration rate and a failure of the anticipated increase in the secretion of aldosterone, as might be expected when the volume contracts in association with sodium depletion.

Hyponatremia and hypochloremia with hypernatruria and hyperchloruria have also been described in patients with various neurologic disorders, including cerebral vascular disease, diffuse encephalitis, bulbar poliomyelitis, head injuries, tumors of the posterior thalamus, and tumors of the fourth ventricle. Such cerebral salt-wasting (encephalogenic hyponatremia), with a paradoxical association of hyponatremia and renal salt-wasting, has more recently also been shown to be secondary to a sustained and inappropriate release of antidiuretic hormone. In such a patient, there was little effect upon the sodium with desoxycorticosterone acetate, while restriction of water when on a sodium-free diet induced a rise in the serum sodium from 125 to 138 mEq./L., with a progressive diminution of the renal excretion of sodium from 100 mEq. daily to less than 2 mEq. daily.

The patient reported herein also demonstrates three very important clues to the early diagnosis of a bronchogenic carcinoma. The first consists of the occurrence of syncope or syncopal-like spells, particularly when associated with of bradycardia. This has been attributed to the pressure on the vagal nerves. It is usually indicative of metastatic spread. The next clinical feature is the severe bone and joint pain that accompanies a bronchogenic carcinoma or many other malignancies throughout the body. The importance of this latter clue is enhanced by the fact that both bronchogenic carcinomas and pleural mesotheliomas have actually been cured following resection of the tumor, to which attention was directed by an astute clinician taking early cognizance of the skeletal symptoms. Finally, the hypereosinophilia is at times a clue to the presence of a bronchogenic carcinoma or some other necrotic neoplasm in the body.

SUMMARY

A third case is reported of a patient with a bronchogenic carcinoma who developed profound hyponatremia and renal sodium loss in the presence of normal kidneys and adrenal glands.

The tenet has been set forth that such an unusual association is due to a prolonged and inappropriate secretion of antidiuretic hormone. Various postulates that might explain such an elaboration of antidiuretic hormone are presented.

It is hoped that future clinical studies of this syndrome may clarify the underlying mechanisms, particularly the role of aldosterone and the possible elaboration of other humoral agents by the tumor.

SUMMARIO IN INTERLINGUA

Le presente articulo es le tertie reporto in le litteratura de un patiente con un carcinoma bronchogene qui disveloppava profunde hyponatremia e hypochloremia in

association con perditas considerabile de tanto natrium como etiam chloruro in le urina. Ab le puncto de vista clinic le function renal e suprarenal esseva normal, e al necropsia nulle significative alterationes pathologic esseva detegite in le renes e

le corpores suprarenal.

Tanto in iste patiente como etiam in duo similes de previe reportos, il pareva que le melior explication del inusual disrangiamento electrolytic esseva le postulato de un continue e inappropriate secretion de hormon antidiuretic. In plus, le disordine pare esser le consequentia del resultante expansion del volumine de liquido corporee. Esseva constatate ni dishydratation de forma clinicamente evidente ni contraction del volumine de liquido corporee con le progredente depletion de natrium e le hypotonicitate del plasma. Es revistate le pathogenese e le possibile factores etiologic in iste syndrome. Il existe un similitude clinic inter iste syndrome e le syndrome de hyponatremia encephalogene. In ambe iste disordines le perdita de natrium e le hyponatremia pote esser prevenite in grande mesura per le restriction del liquido ingerite.

Le presente patiente exhibiva etiam le sequente tres indicios in supporto de un precoce diagnose de carcinoma bronchogene: (1) Episodios syncopoide, particularmente in association con bradycardia; (2) sever dolores ossee e articular, sin detegibile

reflexion roentgenologic; e (3) hypereosinophilia.

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EDITORIAL

THE IMPORTANCE OF EARLY DIAGNOSIS AND TREATMENT OF PHENYLKETONURIA *

In the short space of 25 years since Fölling first identified phenylpyruvic acid in the urine of a mentally retarded patient, our knowledge of phenylketonuria has advanced remarkably. We now have an intimate understanding of its cause at a biochemical level, and as a result of this information, it has been possible to develop an effective means of therapy to prevent the mental deterioration which, until recently, had appeared to be inevitably associated with the metabolic defect.

Phenylketonuria properly belongs in the group of diseases designated "inborn errors of metabolism" by Sir Archibald Garrod.2 The well-documented hereditary pattern of this condition and the recent demonstration of a specific enzyme deficiency in the liver of affected individuals leave no doubt that phenylketonuria is another example of a "genetic defect-enzymatic deficiency" disease in the same category as galactosemia, alcaptonuria and the glycogen storage diseases.

BIOCHEMICAL DEFECT

The biochemical nature of the metabolic defect in phenylketonuria was shown to be in the conversion of phenylalanine to tyrosine.

In 1953 Jervis 8 found that homogenates of liver from normal humans oxidized phenylalanine to tyrosine but that similar preparations from two phenylketonuric patients could not catalyze this reaction. In the same year Udenfriend and Bessman 4 demonstrated that no appreciable labeling occurred in the tyrosine residues of the plasma proteins when phenylketonuric patients were given isotopically labeled phenylalanine.

^{*} From the National Institute of Arthritis and Metabolic Diseases, National Institutes

of Health, U. S. Public Health Service, Bethesda, Maryland.

¹ Fölling, A.: Üeber Ausscheidung von Phenylbrenztraubensäure in den Harn als Stoffwechselanomalie in Verbindung mit Imbezillität, Ztschr. f. physiol. Chem. 227: 169–176,

<sup>1934.
&</sup>lt;sup>2</sup> Garrod, A. E.: Inborn errors of metabolism, 2nd Ed., 1923, H. Frowde and Hodder & Stoughton, Ltd., London.

³ Jervis, G. A.: Phenylpyruvic oligophrenia. Deficiency of phenylalanine oxidizing system, Proc. Soc. Exper. Biol. and Med. 82: 514-515, 1953.

⁴ Udenfriend, S., and Bessman, S. P.: The hydroxylation of phenylalanine and antipyrine in phenylpyruvic oligophrenia, J. Bioi. Chem. 203: 961-966, 1953.

Since then, it has been possible to define the biochemical defect more precisely. Detailed studies on the phenylalanine hydroxylation enzyme system of mammalian liver by Udenfriend and Cooper, Mitoma, and Kaufman have shown that two protein components are required in this oxidation step: a phenylalanine hydroxylase, and an accessory enzyme involved in the cyclic regeneration of a pteridine-like cofactor.8 Wallace, Moldave and Meister 9 and Mitoma, Auld and Udenfriend 10 have analyzed liver fractions from phenylketonuric subjects, and their results indicate that only one of these proteins, the phenylalanine hydroxylase, is missing in the hereditary disease.

GENETIC ASPECTS

Phenylketonuria is inherited as a recessive trait with equal frequency in males and females, and it appears to be transmitted as a single autosomal gene. It is to be expected, therefore, that the affected individuals are homozygotes, and that they have inherited abnormal genes from both heterozygous parents.

During the last few years, several laboratories have studied means of detecting the carrier trait and have demonstrated that parents of phenylketonuric children show a distinctly lower tolerance to a test load of oral l-phenylalanine, as indicated by higher than normal plasma phenylalanine levels during such a test. 11-13 The lower tolerance is presumably due to less phenylalanine hydroxylase activity in the liver of the heterozygote. singer and Knox 14 have found the fasting levels of phenylalanine to be higher in heterozygotes than in a normal group, and they believe that this measurement is as sensitive as the phenylalanine tolerance test in detecting carriers

⁵ Udenfriend, S., and Cooper, J. R.: The enzymatic conversion of phenylalanine to tyrosine, J. Biol. Chem. 194: 503-511, 1952.

⁶ Mitoma, C.: Studies on partially purified phenylalanine hydroxylase, Arch. Biochem. 60: 476-484, 1956.

⁷ Kaufman, S.: The enzymatic conversion of phenylalanine to tyrosine, J. Biol. Chem. 226: 511-524, 1958.

⁸ Kaufman, S.: Phenylalanine hydroxylation cofactor in phenylketonuria, Science 128: 1506-1507, 1958.

⁹ Wallace, H. W., Moldave, K., and Meister, A.: Studies on conversion of phenylalanine to tyrosine in phenylpyruvic oligophrenia, Proc. Soc. Exper. Biol. and Med. 94: 632-633, 1957.

Mitoma, C., Auld, R. M., and Udenfriend, S.: On the nature of the enzymatic defect in phenylpyruvic oligophrenia, Proc. Soc. Exper. Biol. and Med. 94: 634-635, 1957.
 Hsia, D. Y.-Y., Driscoll, K., Troll, W., and Knox, W. E.: Detection by phenylalanine tolerance tests of heterozygous carriers of phenylketonuria, Nature, London 178: 1239-1240, 1956.

 ¹² Hsia, D. Y.-Y., and Paine, R. S.: Phenylketonuria: detection of the heterozygous carrier, J. Mental Deficiency Research 1: 53-65, 1957.
 13 Berry, H., Sutherland, B., and Guest, G. M.: Phenylalanine tolerance tests on rela-

tives of phenylketonuric children, Am. J. Human Genet. 9: 310-316, 1957.

14 Knox, W. E., and Messinger, E. C.: The detection in the heterozygote of the metabolic effect of the recessive gene for phenylketonuria, Am. J. Human Genet. 10: 53-60,

of this condition. Hsia 15 has recently proposed that the ratio of phenylalanine to tyrosine one hour after an oral phenylalanine load is a more reliable index of the carrier trait than the phenylalanine values alone. By these methods the difference between the parents (heterozygotes) group, and the normal non-carrier group is great enough to distinguish two distinct groups. However, the reliability of the phenylalanine tolerance test as a means of detecting the trait in a particular individual is less significant since there is appreciable overlap between the two groups. With refinement of the methods, it may be possible to increase the value of the test in this respect. Further assessment of the range of values within the normal and heterozygous groups, and study of the influence of dietary and other environmental factors on the plasma phenylalanine level are needed to evaluate the usefulness of these methods.

MENTAL DEFICIENCY

The major medical problem in phenylketonuria is the severe mental retardation, until recently unavoidably associated with this disease. Most of the affected individuals are idiots and very few have I.O.'s above 70. majority must be cared for in institutions. Although the cause for the mental deficiency is unknown, in several theories it has been proposed that abnormal metabolites produced from phenylalanine, such as o-hydroxyphenylethylamine might be toxic to the nervous tissue. The high tissue level of phenylalanine itself may interfere with some vital process during the development of the central nervous system. Though the brain of phenylketonuric patients appears to be grossly normal at autopsy, and most pathological examinations have reported no significant changes, Alvord et al.16 described a deficient myelinization of some of the tracts of the central nervous system in two children with this disease. Poser and van Bogaert 17 found multiple areas of altered myelination associated with fibrillary gliosis in the central nervous system of an 18 year old male phenylketonuric patient. They suggest that as a consequence of the metabolic defect there is a disturbance of the glial cell-myelin sheath relationship. Although the sequence of events—phenylalanine oxidation enzyme defect -> accumulation of a toxic agent -> structural derangement during maturation of the central nervous system -> mental retardation-seems to be a logical one, we must realize that, as yet, we have no direct evidence proving that this is the correct mechanism. The hypothesis is, of course, of great value as a stimulus for research in this area.

15 Hsia, D. Y.-Y.: Phenylketonuria: the phenylalanine-tyrosine ratio in the detection

of the heterozygous carrier, J. Mental Deficiency Research 2: 8-16, 1958.

16 Alvord, E. C., Jr., Stevenson, L. D., Vogel, F. S., and Engle, R. L., Jr.: Neuropathological findings in phenylpyruvic oligophrenia (phenylketonuria), J. Neuropath. and Exper. Neurol. 9: 298-310, 1950.

17 Poser, C. M., and van Bogaert, L.: Neuropathic observations in phenylketonuria, Brain 82: 1-9, 1959.

EFFECT OF LOW PHENYLALANINE DIET

The use of a diet low in phenylalanine in treating phenylket nuria was first reported by Bickel et al. 18, 19 and by Woolf et al. 20 in E1. Armstrong and Tyler 21 in this country. The most noticeable changes in the patients were an improvement in neurologic symptoms, better coordinated movements and motor ability, and a decrease in tenseness and irritability. Effects on mental retardation were equivocal, but this was difficult to evaluate because of the beneficial changes in attention and coordination mentioned above. As more cases were treated, particularly those under two years of age, it became evident that favorable effects in preventing mental retardation were obtained and that these were greater in the younger patients.

Knox 22 has recently collected the results of treatment of 28 cases with the low phenylalanine diet started before two years of age. It is remarkable that all six infants started on the diet before eight weeks of age are developing with normal or nearly normal intelligence. It is also evident that the earlier treatment is initiated, the greater the effectiveness of the diet. Treatment started after children are two years old appears to have much less effect upon the oligophrenia, though some gain in intelligence as well as the improvement in motor ability and disposition makes a trial period on the diet worthwhile in the older children.

DIETARY MANAGEMENT

Problems in the administration of a diet low in phenylalanine have recently been expertly discussed by Woolf et al.28 The plasma phenylalanine level has been found to be the best quantitative index of the dietary control achieved, since in untreated phenylketonurics the level may be as high as 40 mg.% whereas in normal individuals it is within 1 to 2 mg.%. It is possible to reduce the level in phenylketonurics to the normal range with the low phenylalanine diet, though a value slightly above this, in the order of 5 mg.%, seems to be a better goal in these patients. By maintaining this higher level, an adequate supply of this essential amino acid is assured at all times during the period of rapid growth.24, 25

- ¹⁸ Bickel, H., Gerrard, J., and Hickmans, E. M.: Influence of phenylalanine intake on phenylketonuria, Lancet 2: 812-813, 1953.
 ¹⁹ Bickel, H., Gerrard, J., and Hickmans, E. M.: The influence of phenylalanine intake on the chemistry and behavior of a phenylketonuric child, Acta pediat. 43: 64-77, 1954.
 ²⁰ Woolf, L. I., Griffiths, R., and Moncrieff, A.: Treatment of phenylketonuria with a diet low in phenylalanine, Brit. M. J. 1: 57-64, 1955.
 ²¹ Armstrong, M. D., and Tyler, F. H.: Studies on phenylketonuria. I. Restricted phenylalanine intake in phenylketonuria, J. Clin. Investigation 34: 565-580, 1955.
 ²² Know W. E.: Personal communication.

- phenylatanine intake in phenylateronuria, J. Chin. Investigation 34: 305-380, 1955.

 ²² Knox, W. E.: Personal communication.

 ²³ Woolf, L. I., Griffiths, R., Moncrieff, A., Coates, S., and Dillistone, F.: The dietary treatment of phenylketonuria, Arch. Dis. Childhood 33: 31-45, 1958.

 ²⁴ Paine, R. S., and Hsia, D. Y.-Y.: The dietary phenylalanine requirements and tolerances of phenylketonuric patients, J. Dis. Child. 94: 224-230, 1957.

 ²⁵ Berry, H. K., Sutherland, B. S., Guest, G. M., and Umbarger, B.: Chemical and clinical observations during treatment of children with phenylketonuria, Pediatrics 21: 929-

Failure to find phenylpyruvic acid in the urine is not sufficient evidence of optimal dietary control.

In the first studies with low phenylalanine diets, it was necessary either to prepare them by hydrolyzing casein and treating the hydrolysate with charcoal to remove phenylalanine 18 or to use the expensive alternative of a synthetic diet of pure amino acids, etc. 21 This was necessary because most food proteins contain about 5% phenylalanine, and none of them has a sufficiently low content of this amino acid. Fortunately, low phenylalanine diets are now available commercially.* There is a need for further improvement in the taste and odor to make the diet more acceptable, particularly to older children.

The length of time that it is necessary to keep children on the special diet has not been definitely established though data on this point are being collected at the present time by various investigators. It seems probable that a permanent dietary regimen will not be necessary. It is hoped that by proper control during the first two years the most critical period will be passed. Perhaps after this time the sensitivity of the central nervous system to high levels of phenylalanine may gradually decrease and within another year or two, the special diet may be safely modified or eliminated.

DIAGNOSIS

Early diagnosis and treatment of this condition are vital to obtain the maximum benefit from the low phenylalanine diet. For this reason, greater awareness of the condition and familiarity with the presumptive and confirmatory tests are necessary.

Finding new cases within a family with known phenylketonuria should be a relatively simple problem, and since the chances are one in four of another sibling in such a family being affected, an infant with this background should be very carefully examined. It is estimated that about 1:25,000 new births will have phenylketonuria and that the frequency of the carrier of this disease in the general population is 1:70.

Approximately 1% of the population in our mental institutions have this condition. It is, therefore, a public health problem of considerable importance. During the last year, two conferences have been held by the Division of Health Services of the Children's Bureau in the Department of Health, Education, and Welfare on the problems of early detection and treatment of phenylketonuria.† A number of new case detection screening programs within selected state institutions, well baby clinics and retarded children clinics have been organized and the results of these surveys will be evaluated by this group. In addition, the Committee is compiling

^{*}Two commercially available low phenylalanine diets are Ketonil, from Merck Sharp and Dohme, and Lofenalac, from Mead-Johnson.

[†]The Technical Committee on Clinical Programs for Mentally Retarded Children, Division of Health Services, Children's Bureau, Social Security Administration, U. S. Department of Health, Education, and Welfare, Washington, D. C.

data on diagnostic procedures and on the dietary treatment, and this information will be distributed to physicians interested in the problem.

PRESUMPTIVE TESTS

The presumptive tests for phenylketonuria depend upon the presence of phenylpyruvic acid in the urine. The most common tests are the formation of a green color in the presence of ferric chloride. 26-28 and the precipitation of the phenylhydrazone derivative of phenylpyruvic acid with 2,4-dinitrophenylhydrazine.29

The recommended office procedure for detecting the urinary phenylpyruvic acid is as follows: 80 Add three to five drops of 10% ferric chloride to 1 c.c. of urine (without prior acidification) and note the color change immediately and for the following three or four minutes. Normal urine may become dark vellow or amber. Phenylketonuric urine turns green rapidly and then the color gradually fades. The use of the concentrated ferric chloride reagent recommended here gives a more sensitive test than that described in most textbooks, but the color fades quickly, and it must be observed immediately after the ferric chloride is added. In office practice and in clinics it is often more practical to place a drop or two of the ferric chloride solution directly on a recently wet diaper than to obtain a urine specimen. A simple "stick test" suitable for either urine or wet diapers is now available commercially.* It is not necessary to analyze urine immediately after it is voided though positive urine samples may become negative due to bacterial decomposition of the phenylpyruvic acid. An ingenious method has been employed by Dr. Guest and Dr. Berry in Cincinnati in which urine samples are dried on filter paper, and sent by mail to a central diagnostic laboratory.

The presence of a positive ferric chloride test is presumptive evidence for phenylketonuria, but other substances also give a positive reaction, such as chlorpromazine and aspirin. It must also be remembered that a phenylketonuric child may occasionally give a negative urine test, and for this reason a single negative examination is not sufficient evidence to exclude this disease.

CONFIRMATORY TESTS

In all cases suspected of being phenylketonuric on the basis of a positive ferric chloride test in the urine, the diagnosis should be confirmed by meas-

²⁶ Berry, J. P., and Woolf, L. I.: Estimation of phenylpyruvic acid, Nature, London
 169: 202-203, 1952.
 ²⁷ The, T. P., Fleury, P., and Vink, C. L. J.: Determination of phenylpyruvic acid in

the urine of patients with oligophrenia phenylpyruvica, Clin. Chim. Acta 2: 424-428, 1957.

²⁸ Saifer, A., and Harris, A. F.: Studies on the photometric determination of phenylpyruvic acid in urine, Clin. Chem. 5: 203-217, 1959.

²⁹ Penrose, L., and Quastel, J. H.: Metabolic studies in phenylketonuria, Biochem. J. 31: 266-274, 1937.

30 Centerwall, W. R.: An evaluation of testing methods used for phenylketonuria. A paper read before the 87th Annual Meeting of the American Public Health Association, Atlantic City, New Jersey, October 19-23, 1959.
 *A product called Phenistix is produced by the Ames Company, Inc.

urement of the level of phenylalanine in the blood. Several methods are available to determine plasma or serum phenylalanine. It may be enzymatically converted to phenylethylamine and the latter measured colorimetrically after reaction with methyl orange. 31 Phenylalanine may also be separated from other amino acids by paper chromatography after deproteinization of plasma and the amount estimated by the intensity of the color spot after reaction with ninhvdrin.32 It can also be measured directly in serum by converting it enzymatically to phenylpyruvic acid and measuring the latter spectrophotometrically as the enol-borate complex.⁸³ These methods are also suitable to follow the level of phenylalanine in the blood of patients on the low phenylalanine diet.

It has been shown recently that in phenylketonuria, the plasma phenylalanine level rises within a few hours after birth and that it is well above the normal range of values within one day.84 In contrast, there may be delay of from several days up to three weeks or more before phenylpyruvic acid appears in the urine. For this reason, measuring the blood phenylalanine level in newborn infants in families with known phenylketonuria would permit an earlier diagnosis and avoid unnecessary delay in starting

the special diet.

SUMMARY

Recent experience with a low phenylalanine diet provides convincing evidence that the mental retardation usually associated with phenylketonuria is a preventable consequence of this metabolic disease, provided the treatment is started early. Ideally this would be within the first few weeks after birth. The benefits to be gained by the dietary treatment will be progressively less the longer the child goes without treatment. Although the diet has no effect upon the inherited metabolic defect; it prevents the oligophrenia and the neurologic symptoms found in untreated cases.

The importance of early diagnosis and treatment cannot be overemphasized, and the simple ferric chloride test of the urine should be a routine procedure in young children. Years ago ferric chloride was used in every physician's office to detect acetone bodies, but in recent years this test has been gradually replaced by other methods. It is hoped that physicians will put the bottle of ferric chloride back on their reagent shelf for this new purpose.

BERT N. LA DU, M.D., Ph.D.

84 Armstrong, M. D.: Personal communication.

⁸¹ Udenfriend, S., and Cooper, J. R.: Assay of L-phenylalanine as phenylethylamine after enzymatic decarboxylation; application to isotope studies, J. Biol. Chem. 203: 953-960, 1953.

Berry, H. K.: Paper chromatographic method for estimation of phenylalanine, Proc. Soc. Exper. Biol. and Med. 95: 71-73, 1957.
 La Du, B. N., and Michael, P. J.: An enzymatic spectrophotometric method for the determination of phenylalanine in blood, J. Lab. and Clin. Med., in press.

REVIEWS

The Essentials of Roentgen Interpretation. By Lester W. Paul, M.D., and John H. Juhl, M.D. 839 pages; 27.5 × 20 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1959. Price, \$25.00.

The Essentials of Roentgen Interpretation offers the physician guidance for the use of radiography in the daily practice of medicine. Major space is devoted to the osseous system, gastrointestinal tract, and the intrathoracic organs. The central nervous system, genito-urinary tracts, and maxillo-facial region are considered in

less extensive but adequate subdivisions.

Methodology is described when indicated, but technical details are kept to a minimum in the interests of brevity and clarity. The illustrations are well marked and can be interpreted easily. Close integration between pictures and text exists throughout the book. Common problems in which radiologic methods are of value are emphasized, and representative radiographic studies of these conditions are presented. Unusual or rare diseases are described briefly; if characteristic roent-genograms exist they are included. The utility of the book is increased by a good index and pertinent references to the literature.

This informative book contains an enormous amount of factual material, presented in clear and concise style. The value of radiographic studies in various unusual problems, such as reticuloendotheliosis or metabolic diseases, is assessed. This aids in selecting appropriate procedures for investigating a given patient. By such guidance time and money may be saved. The doctors to whom the authors have addressed themselves—namely, those not specializing in radiology—will appreciate

the effort. To these physicians the book is recommended.

J. E. C.

Vertigo and Dizziness. (Modern Medical Monographs 15; Editor-in-Chief: IRVING S. WRIGHT, M.D.) By BERNARD J. ALPERS, M.D., Sc.D. (Med.). 120 pages; 20 × 27.5 cm. Grune and Stratton, Inc., New York. 1958. Price, \$5.00.

This monograph constitutes a most complete consideration of the factors involved in the symptom of vertigo. The author presents his material in a systematic fashion beginning with the anatomy and physiology of the labyrinth and its central connections. There is then a consideration of the symptoms and causes of vertigo. The volume is concluded with a discussion of diagnosis and treatment of this troublesome symptom.

Throughout the monograph when the author encounters a controversial point, he is careful to present all points of view and the evidence for such conclusions, but refrains from injecting his own opinion. As a result, this volume points up the inconclusiveness of much of our knowledge regarding the labyrinthine system and

its affections.

All physicians will find this monograph of interest, if only to reassure them that their own uncertainty regarding vertigo is a condition shared by all. The sections on diagnosis and treatment will be of particular interest to the practicing physician.

There are a few drawings in the section on anatomy and in the remainder of the book there are a few tables. The bibliography located at the end of the volume is quite complete and will be useful to any reader who wishes to read further on this subject. Additionally, there is a useful index.

C. V. B.

X-ray and Radium in Dermatology. (Publication No. 349, American Lecture Series.)
By Bernard A. Wansker, M.D. 114 pages; 22.5 × 14.5 cm. Charles C
Thomas, Publisher, Springfield, Illinois. 1959. Price, \$5.00.

The subjects discussed in this book are physics, circuits, physical factors, filtered x-ray technic, biology, low-voltage therapy, specific methods of x-ray therapy,

contact therapy, Grenz rays, cathode rays, radium, and radioisotopes.

This is a fair summary of dermatologic radiotherapy. In general terms it can be said that this has the characteristics of many works in dermatologic radiotherapy—it is based on empirical procedures disregarding the requirements of modern radiotherapy in radiobiology, dosimetry, and technics.

The dosages advised as a goal in skin carcinoma are higher than necessary to cure tumors, therefore increasing the chances of late changes and necrosis of the

normal tissues.

The chapter on cathode rays (electron beam therapy) does not give a clear idea

of their application or main possibilities of usage in modern therapy.

The chapter on radium therapy is very short in details of dosimetry which is indispensable for the administration of a proper therapy. The measure of the dose in roentgens or rads is an indispensable requirement; it is the only way which makes technics of treatment consistent and reproducible.

The H.v.l. for radium is 12 mm. of lead; the use of 3 mm. for protection of sensitive structures as advised in the book will only give a false sense of security to the therapist. Protection by lead in radium therapy is seldom possible due to the

heavy shield necessary and the short treatment distance used.

It will be desirable to keep a closer association between dermatologist and radiotherapist in order that they may benefit reciprocally from their investigations and experiences.

FERNANDO G. BLOEDORN, M.D.

Practical Dermatology. 2nd Ed. By George M. Lewis, M.D., F.A.C.P. 363 pages; 25.5 × 16 cm. W. B. Saunders Co., Philadelphia. 1959. Price, \$8.00.

The second edition of Lewis' Practical Dermatology contains approximately 350 pages and over 500 illustrations in black and white, which are conveniently and practically placed near the subject matter. There are also under the photographs short, pointed, descriptive captions. Essentially all the common dermatoses are briefly covered and described, especially as to etiology, symptoms, clinical picture, and treatment. There is a tendency for the author to stick somewhat to the older forms of treatment, but he has also readily accepted most of the newer forms, some of which have already been found inadequate. It is difficult in these days to keep treatment current in any textbook. For instance, the book does not contain the treatment of superficial fungus infection with griseofulvin because this form of treatment came out at about the time the text was published. This form of treatment makes out of date that of x-ray epilation of scalps, included in the book. The author recognized this type of deficiency in textbooks.

Interesting are the chapters on dermatologic therapy. Quite an innovation in a textbook of this size is the chapter on the basic sciences in dermatology. Also of

interest is the short bibliography which should be helpful to the more advanced student.

In summary, Lewis' second edition of *Practical Dermatology* has brought up to date the first edition. The text should prove to be a very practical book for the general practitioner and the early student in dermatology.

F. A. E

Recent Advances in Cerebral Palsy. Edited by R. S. Illingworth, M.D., F.R.C.P., D.P.H., D.C.H. 413 pages; 24 × 16 cm. Little, Brown and Company, Boston. 1958. Price, \$10.00.

This volume consists of contributions by specialists in various aspects of the problem of the brain damaged child. Most of the contributors are from the United Kingdom but others are from the United States and Australia. Although the editor is a pediatrician, the contributors include two other pediatricians, one neuropathologist, two psychologists, one educator of the deaf, four orthopedists, two speech therapists and one neurosurgeon. The variation of vocations of these workers points up very well the team-work necessary in the management of the various disorders which are included under the term "cerebral palsy." The editor concerns himself with etiology, diagnosis, and classification of the patient. His discussion is concerned primarily with the child of school age, since this is apparently the area in which he is most experienced. The other writers provide sections on treatment and its various aspects, which includes neurosurgical and orthopedic surgical treatment, the use of drugs and physical therapy, as well as the management of deafness and speech disturbances. There is an appendix which lists the various voluntary and tax supported agencies in the United States which deal with this problem. This appendix complements a similar chapter in the book which outlines such agencies in the United Kingdom.

This volume is well illustrated and, following each chapter, there is a quite complete bibliography. The volume index is limited and would not appear to be very useful.

The book is a first-rate summary of the more recent thinking of workers who are intimately concerned with this problem. It will be of interest to all medical personnel. It is doubtful if much of the information present will be news to persons immediately concerned with this problem but students, both medical and paramedical, will find this book of value.

C. V. B.

Modern Trends in Pathology. Edited by Douglas H. Collins, O.B.E., M.D. (L'pool), F.R.C.P. (Lond.). 346 pages; 25 × 17 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1959. Price, \$15.00.

The book is composed of a mixed salad of subjects by various authors often with little interrelationship between them. Many of the chapters miss the most significant recent findings. The opening chapter drawing heavily on electron microscopic findings only succeeds in whetting the appetite. The important contributions of this method to our knowledge of the various nephroses would have been more appropriate. The study of tissues in the fresh state is interesting but contributes little in comparison to current developments in quantitative tissue culture methods. "The Localization of Antibody Production" is obsolete in view of present fluorescent

labelled a trigen-antibody methods. The chapter on "The Human Adrenal Cortex in Disease" is particularly limited. Although this reviewer agrees with the concept of production of certain hormones by separate zones of the adrenal cortex, the author's presentation seems both ill-founded and confused. The chapter by Willis of "Some Uncommon and Recently Identified Tumors" is useful but hardly to be regarded as a "modern trend." The chapter on "The Pathological Relationships of 5-Hydroxy-tryptamine" is one of the more appropriate inclusions. Chapters on the application or evaluation of histochemical procedures or autoradiography, without doubt two of the major "modern trends" in pathology, are most conspicuously absent.

In short, although the book may describe trends in pathology, many are minor

and few are modern.

HARLAN I. FIRMINGER, M.D.

Penicillin. (Antibiotic Monographs, No. 9.) By Harold L. Hirsh, M.D., and Lawrence E. Putnam, M.D. 148 pages; 23.5 × 16 cm. Medical Encyclopedia, Inc., New York. 1958. Price, \$4.00.

This monograph by Dr. Hirsh and Dr. Putnam is one of several recent Medical Encyclopedia publications on antibiotics. The authors have succeeded in summarizing up-to-date information on the nature and practical application of penicillin. Fifteen years of clinical experience with penicillin have revealed that this antimicrobial is truly one of the most remarkable drugs. Organisms against which penicillin exhibits its greatest degree of activity are inhibited by minute amounts of the drug and the profound effect of this antibiotic against streptococci, pneumococci, gonococci and treponemes has been demonstrated repeatedly throughout the world. Of greatest significance is the apparent inability of these organisms to develop resistance to penicillin. Diseases which once constituted major medical problems and resulted in substantial loss of human life are now readily controlled by the use of penicillin. Although there has been an increase in serious reactions to penicillin, hypersensitivity to this antibiotic is still relatively rare and the tolerant

patient may be given enormous amounts of drug without untoward effect.

The authors have wisely oriented the book for clinicians, emphasizing the methods of treating infections caused by organisms sensitive to penicillin. The relative usefulness of penicillin and other antibiotics in various infectious diseases is only implied in the authors' detailed analysis of illnesses which are highly responsive to penicillin therapy. Development and historical considerations, in vitro antimicrobial activity, pharmacology and dosage forms of the penicillins have been considered very concisely and adequately in the first 30 pages of the monograph. Clinicians will find useful a tabulation of the penicillin sensitivity of various microorganisms and graphs depicting serum concentrations of penicillins administered by different routes. The chapters which follow deal with specific details of the treatment of pneumococcal, streptococcal, staphylococcal, gonococcal and meningococcal and treponemal infections. Schedules of suggested dosage are included in each of these sections and the authors have pointed out the inadequacies of certain types of therapeutic regimens in the management of severe or sequestered infections. In addition, there is a chapter dealing with miscellaneous infections including leptospirosis, rat bite fever, diphtheria, tetanus, anthrax and actinomycosis. Where the effectiveness of penicillin remains controversial, the authors have been careful to emphasize this point and have refrained from expressing personal opinions in this regard. The final chapter deals with phenoxymethyl penicillin in which an attempt has been made to summarize the current concepts of its clinical application.

Dr. Hirsh and Dr. Putnam are to be commended on their selection of material and the supporting bibliography. The essentials of penicillin therapy have been covered thoroughly in this well written monograph. Clinicians, students and workers in the fields of antibiotic research and bacterial infections will find this book a most useful addition to the antibiotic monograph series.

FRED R. McCRUMB, JR., M.D.

BOOKS RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

August, 1959

- Adaptation to Extrauterine Life: Report of the Thirty-first Ross Conference on Pediatric Research. 94 pages; 23 × 15 cm. (paper-bound). 1959. Ross Laboratories, Columbus, Ohio. Available on request.
- Applied Pharmacology (Clark). 9th Ed. By Andrew Wilson, M.D., Ph.D., F.R.F.P.S., Professor of Pharmacology and General Therapeutics, University of Liverpool, etc.; and H. O. Schild, M.D., Ph.D., D.Sc., Reader in Pharmacology in the University of London at University College, London. 750 pages; 23 × 14.5 cm. 1959. Little, Brown and Company, Boston. Price, \$10.00.
- Disability Days, United States, July 1957-June 1958: Statistics on Volume of Restricted-Activity Days, Bed-Disability Days, Work-Loss Days, and School-Loss Days by Age, Sex, Residence, Family Income, Major Activity, and Colendar Quarter. Based on Data Collected in Household Interviews During the Period, July 1957-June 1958. Health Statistics from the U. S. National Health Survey, Series B-10. 68 pages; 26 × 20 cm. (paper-bound). 1959. U. S. Department of Health, Education, and Welfare, Public Health Service, Washington, D. C. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 40¢.
- Early Diagnosis. By various authors; edited by Henry Miller, M.D., F.R.C.P., Physician in Neurology, Royal Victoria Infirmary, Newcastle upon Tyne. 400 pages; 22.5 × 14 cm. 1959. The Williams and Wilkins Company, Baltimore. Price, \$6.50.
- Handbook of Physiology: A Critical, Comprehensive Presentation of Physiological Knowledge and Concepts. Section 1: Neurophysiology. Volume I. Editor-in-Chief: John Field; Section Editor: H. W. Magoun; Executive Editor: Victor E. Hall. 779 pages; 29 × 22 cm. 1959. Published by American Physiological Society, Washington, D. C., and distributed by The Williams & Wilkins Company, Baltimore. Price, \$22.00.
- The Kinetics of Cellular Proliferation. Edited by Frederick Stoheman, Jr., M.D. 456 pages; 26 × 17.5 cm. 1959. Grune & Stratton, New York. Price, \$5.75.
- Preventive Aspects in the Teaching of Pathology: Seventh Report of the Expert Committee on Professional and Technical Education of Medical and Auxiliary Personnel. World Health Organization Technical Report Series No. 175. 30

- pages; 24 × 16 cm. (paper-bound). 1959. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 30¢.
- Role of Hospitals in Ambulatory and Domiciliary Medical Care: Second Report of the Expert Committee on Organization of Medical Care. World Health Organization Technical Report Series No. 176. 32 pages; 24 × 16 cm. (paperbound). 1959. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 30é.
- Thyroid Radioiodine Uptake Measurement: A Standard System for Universal Intercalibration. ORINS-19, U. S. Atomic Energy Commission Report. Marshall Brucer, M.D., Chairman, The Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee. 323 pages; 26.5 × 20.5 cm. (paper-bound). 1959. Oak Ridge Institute of Nuclear Studies, Inc., Oak Ridge, Tennessee. Price, \$3.50; available from the Office of Technical Services, Department of Commerce, Washington, 25, D. C.
- What Next, Doctor Peck? By Joseph H. Peck, M.D. 209 pages; 21 × 14 cm. 1959. Prentice-Hall, Inc., Englewood Cliffs, N. J. Price, \$3.50.
- The Year Book of Cancer (1958-1959 Year Book Series). Compiled and edited by RANDOLPH LEE CLARK, JR., B.S., M.D., M.Sc. (Surgery), D.Sc. (Hon.), Houston, Texas, Director and Surgeon-in-Chief, The University of Texas M. D. Anderson Hospital and Tumor Institute, etc.; and RUSSELL W. CUMLEY, B.A., M.A., Ph.D., Houston, Texas, Director of Publications, The University of Texas M. D. Anderson Hospital and Tumor Institute, etc. 570 pages; 20 × 13.5 cm. 1959. The Year Book Publishers, Chicago. Price, \$8.00.

September, 1959

- Anatomy of the Human Body. 27th Ed. By Henry Gray, F.R.S., Late Fellow of the Royal College of Surgeons, etc. Edited by Charles Mayo Goss, M.D., Managing Editor of the Anatomical Record, etc. 1,458 pages; 27 × 17 cm. 1959. Lea & Febiger, Philadelphia. Price, \$17.50.
- The Arterial Wall. Edited by Albert I. Lansing, A.B., Ph.D., Chairman, Department of Anatomy, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania. Sponsored by The Gerontological Society, Inc. 259 pages; 23.5 × 15.5 cm. 1959. The Williams & Wilkins Company, Baltimore. Price, \$7.50.
- Clinical Auscultation of the Heart. 2nd Ed. By Samuel A. Levine, M.D., Sc.D. (Hon.), F.A.C.P., Clinical Professor of Medicine, Emeritus, Harvard Medical School, etc.; and W. Proctor Harvey, M.D., Associate Professor of Medicine, Georgetown University School of Medicine and Director, Division of Cardiology, Georgetown University Hospital, etc. 657 pages; 25.5 × 17 cm. 1959. W. B. Saunders Company, Philadelphia. Price, \$11.00.
- Clinical Disorders of Hydration and Acid-Base Equilibrium. 2nd Ed. By Louis G. Welt, M.D., Professor of Medicine, Department of Medicine, University of North Carolina. 336 pages; 22 × 15 cm. 1959. Little, Brown and Company, Boston. Price, \$7.00.

- Clinical Scalar Electrocardiography. 4th Ed. By Bernard S. Lipman, A.B., M.D., F.A.C.P., Associate in Medicine, Emory University School of Medicine, etc.; and Edward Massie, A.B., M.D., F.A.C.P., Associate Professor of Clinical Medicine, Washington University School of Medicine, etc. 474 pages; 22.5 × 14.5 cm. 1959. Year Book Publishers, Inc., Chicago. Price, \$8.00.
- Cold Injury, Ground Type. Medical Department, United States Army. Prepared under the direction of Major General S. B. Hays, The Surgeon General, United States Army. Editor in Chief: Colonel John Boyd Coates, Jr., MC; Associate Editor: Elizabeth M. McFetridge, M.A. By Colonel Tom F. Whayne, MC, USA (Ret.), Professor of Preventive Medicine, School of Medicine, University of Pennsylvania, Philadelphia, Pa.; and Michael E. Debakey, M.D., Professor of Surgery and Chairman of the Department, Baylor University College of Medicine, Houston, Tex., formerly Colonel, MC, AUS. 570 pages; 25.5 × 17.5 cm. 1958. Office of the Surgeon General, Department of the Army, Washington, D. C. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C. at \$6.25 (buckram).
- Color Atlas and Management of Vascular Disease. By WILLIAM T. FOLEY, M.D., F.A.C.P., Associate Professor of Clinical Medicine, Cornell University Medical College, etc.; and IRVING S. WRIGHT, M.D., F.A.C.P., Professor of Clinical Medicine, Cornell University Medical College, etc. 170 pages; 26 × 19.5 cm. 1959. Appleton-Century-Crofts, Inc., New York. Price, \$18.00.
- Cutaneous Manifestations of the Malignant Lymphomas. (Publication Number 330, American Lecture Series; a monograph in The Bannerstone Division of American Lectures in Dermatology; edited by Arthur C. Curtis, M.D., Chairman, Department of Dermatology and Syphilology, University of Michigan Medical School, Ann Arbor, Michigan.) By Samuel M. Bluefare, B.S., M.D., F.A.C.P., Associate Professor of Dermatology, Northwestern University Medical School, etc.; with an introduction by Steven O. Schwartz, M.D. 534 pages; 22.5 × 14.5 cm. 1959. Charles C Thomas, Publisher, Springfield, Illinois. Price, \$15.50.
- Diseases of Medical Progress: A Survey of Diseases and Syndromes Unintentionally Induced as the Result of Properly Indicated, Widely-accepted Therapeutic Procedures. By Robert H. Moser, B.S., M.D., Major, Medical Corps, U. S. Army, etc.; with a foreword by F. Dennette Adams, M.D., Physician, Board of Consultation, Massachusetts General Hospital. 131 pages; 22.5 × 14 cm. 1959. Charles C Thomas, Publisher, Springfield, Illinois. Price, \$4.75.
- Expéditions françaises à l'Himalaya: Aspect médical. Comité de l'Himalaya, Comité Scientifique du Club Alpin Français. By Jean Rivolier; with the collaboration of P. Biget, F. Florence, A. Lapras and J. Oudot. 229 pages; 24 × 17.5 cm. (paper-bound). 1959. Hermann, Paris. Price, 3.000 fr.
- Expert Committee on Hygiene and Sanitation in Aviation: First Report. World Health Organization Technical Report Series No. 174. 62 pages; 24 × 16 cm. (paper-bound). 1959. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 60 cents.

- Iron Deficiency Anaemia: Report of a Study Group. World Health Organization Technical Report Series No. 182. 15 pages; 24 × 16 cm. (paper-bound). 1959. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30 cents.
- The Life and Times of Sir Charles Hastings, Founder of the British Medical Association. By WILLIAM H. McMenemey, M.A., D.M., F.R.C.P., D.P.M. 516 pages; 23 × 16.5 cm. 1959. Williams & Wilkins Company, Baltimore, exclusive U. S. agents. Price, \$10.00.
- Limitation of Activity and Mobility Due to Chronic Conditions, United States, July 1957-June 1958: Statistics on Prevulence of Limitation of Activity and Mobility Among Persons with One or More Chronic Conditions by Age, Sex, Residence, Family Income, and Major Activity. Based on Data Collected in Household Interviews During the Period July 1957-June 1958. Health Statistics from the U. S. National Health Survey, Series B-11. Public Health Service Publication No. 584-B11. 40 pages; 26 × 20 cm. (paper-bound). 1959. U. S. Department of Health, Education, and Welfare, Public Health Service, Washington, D. C. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 30 cents.
- Master Your Tensions and Enjoy Living Again. By George Stevenson, M.D., and Harry Milt. 241 pages; 23.5 × 15.5 cm. 1959. Prentice-Hall, Inc., Englewood Cliffs, New Jersey. Price, \$4.95.
- Open Reduction of Common Fractures. Modern Surgical Monographs 2. Editor in Chief: I. S. RAVDIN, M.D.; Consulting Editor: RICHARD H. ORR, M.D. By OSCAR P. HAMPTON, JR., M.D., F.A.C.S., Assistant Professor, Clinical Orthopedic Surgery, Washington University School of Medicine, St. Louis; and WILLIAM T. FITTS, JR., M.D., F.A.C.S., Professor of Surgery, Schools of Medicine, University of Pennsylvania, Philadelphia, etc. 212 pages; 23.5 × 15.5 cm. 1959. Grune & Stratton, New York. Price, \$8.75.
- The Physiology and Treatment of Peptic Ulcer. J. Garrott Allen, Editor; Charles B. Clayman, Robert V. De Vito, Henry N. Harkins, Paul C. Hodges, Joseph B. Kirsner, John H. Landor, Harry A. Oberhelman, Jr., Walter L. Palmer, Stanley P. Rigler, Edward H. Storer and Edward R. Woodward. 236 pages; 24 × 16 cm. 1959. University of Chicago Press, Chicago. Price, \$7.50.
- Recent Advances in Cardiology. 5th Ed. By Terence East, M.A., D.M., F.R.C.P., Physician, and Physician-in-charge of Cardiological Department, King's College Hospital; and Curtis Bain, M.C., D.M., F.R.C.P., Consulting Physician, Harrogate General Hospital. Little, Brown and Company, Boston. Price, \$10.00.
- Social Psychiatry and Community Attitudes: Seventh Report of the Expert Committee on Mental Health. World Health Organization Technical Report Series No. 177. 40 pages; 24 × 16 cm. (paper-bound). 1959. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30 cents.
- The Surgeon and the Child. By WILLIS J. POTTS, M.D., Surgeon in Chief, Children's Memorial Hospital, Chicago, etc. 255 pages; 24 × 16 cm. 1959. W. B. Saunders Company, Philadelphia. Price, \$7.50.

- Symposium on Pulmonary Ventilation, Held in Leeds on February 19, 1958, under the Auspices of The British Journal of Anaesthesia. Edited by Dr. R. P. Harbord and Professor R. Woolmer. 109 pages; 23 × 14.5 cm. 1959. The Williams & Wilkins Company, exclusive U. S. agents, Baltimore. Price, \$4.00.
- The Year Book of Medicine (1959-1960 Year Book Series). Edited by Paul B. Beeson, M.D., Carl Muschenheim, M.D., William B. Castle, M.D., Tinsley R. Harrison, M.D., Franz J. Ingelfinger, M.D., and Philip K. Bondy, M.D. 733 pages; 22 × 14 cm. 1959. The Year Book Publishers, Chicago. Price, \$8.00.

COLLEGE NEWS NOTES

BOOKS DONATED TO THE COLLEGE LIBRARY OF PUBLICATIONS BY MEMBERS

Darrell C. Crain, M.D., F.A.C.P., Washington, D. C., HELP FOR TEN MIL-LION, published by J. B. Lippincott Company, Philadelphia, Pa., 1959, 350 pages.

Harold E. Himwich, M.D., F.A.C.P., Galesburg, Ill., and Max Rinkel, M.D., Boston, Mass., INSULIN TREATMENT IN PSYCHIATRY, published by The Philosophical Library, New York, N. Y., 1959, 386 pages.

William S. Hoffman, Ph.D., M.D., F.A.C.P., Chicago, Ill., THE BIOCHEM-ISTRY OF CLINICAL MEDICINE, Second Edition, published by The Year Book Publishers. Chicago. Ill., 1959, 734 pages.

Jonathan C. Meakins, M.D., M.A.C.P., Montreal, Canada, PRACTICE OF MEDICINE, Sixth Edition, published by The C. V. Mosby Company, St. Louis, Mo., 1959, 1916 pages.

Irvine H. Page, M.D., F.A.C.P., Cleveland, Ohio, CONNECTIVE TISSUE, THROMBOSIS, AND ATHEROSCLEROSIS, published by Academic Press, New York and London, 1959, 316 pages.

Eugene P. Pendergrass, M.D., F.A.C.P., J. Parsons Schaeffer, M.D., Ph.D., and Philip J. Hodes, M.D., Philadelphia, Pa., THE HEAD AND NECK IN ROENT-GEN DIAGNOSIS, Volumes I and II, Second Edition, published by Charles C. Thomas, Springfield, Ill., 1956, 1759 pages.

Eugene P. Pendergrass, M.D., F.A.C.P., Philadelphia, Pa., THE PNEUMO-CONIOSIS PROBLEM, published by Charles C. Thomas, Springfield, Ill., 1959, 146

Leandro M. Tocantins, M.D., F.A.C.P., Philadelphia, Pa., PROGRESS IN HEMATOLOGY, Volume II, published by Grune & Stratton, New York, N. Y., 1959, 290 pages.

The College acknowledges with pleasure the following new Life Member:

Dr. Charles M. Caravati, Richmond, Va.

NEW DIRECTORY, AMERICAN COLLEGE OF PHYSICIANS

The 1959 edition of the Directory of the College is approaching publication. It will contain some fourteen hundred pages and represents an enormous amount of editorial work. Many members have placed pre-publication orders at \$9.00, and their copies will be delivered at the earliest possible time after publication. The post-publication price will be \$12.00.

SUPPLEMENT TO CUMULATIVE INDEX, ANNALS OF INTERNAL MEDICINE

A complete cumulative index to the Annals of Internal Medicine, Volumes 1 through 40 (July, 1927-June, 1954) was published in 1956. A Supplement thereto for Volumes 41 through 50 (July, 1954-June, 1959) is now in course of publication. This Supplement will be available on a complimentary basis, on written request, to members of the College and to libraries which are subscribers to the journal. To others, it will be available on a cost-of-publication basis.

THE AMERICAN SOCIETY OF INTERNAL MEDICINE

At the Board of Trustees meeting of the American Society of Internal Medicine held in Omaha, Nebraska, on October 30, 1959, two new component societies were formally admitted to membership.

The Colorado Society, consisting of 196 members, was represented at the meeting. Its officers are as follows:

| President | Secretary | | |
|----------------------------------|--------------------------------------|--|--|
| Robert T. Porter, M.D., F.A.C.P. | Robert V. Elliott, M.D., (Associate) | | |
| 1801—17th Street | 1601 Downing Street | | |
| Greeley, Colorado | Denver 18, Colorado | | |

The Iowa Society, consisting of 99 members, was also represented at the meeting. Its officers are as follows:

| President | Secretary |
|---|---|
| George E. Montgomery, M.D., (Associate) McFarland Clinic | John R. Kersten, M.D. 1235 Fifth Avenue, South |
| Ames, Iowa | Fort Dodge, Iowa |

This brings the total membership of the American Society of Internal Medicine to over 6,200 members with forty-six active component societies. It is anticipated that several more societies will be admitted prior to the Annual Meeting of the American Society scheduled in San Francisco on April 3, 1960.

GRANTS FOR PEDIATRIC RESEARCH

The awards committee for the Mead Johnson Program for Pediatric Research of the American Academy of Pediatrics announced the availability for the coming year of funds to provide financial aid to young pediatric workers. These funds have been provided each year since 1958 by Mead Johnson & Company under rules established by the academy's awards committee.

The maximum amount for any one grant in any year is \$3,500. Grant applicants should be young pediatricians who are not more than ten years beyond the completion of their residency. These grants are specifically intended to encourage the young, unestablished, research-minded, academic pediatrician. Deadline for receipt of grant applications for July, 1960, will be January 15, 1960.

Interested persons should write to American Academy of Pediatrics, 1801 Hinman Avenue, Evanston, Ill.

EUGENE B. FERRIS, JR., MEMORIAL AWARD

Beginning in September, 1959, and continuing each year thereafter, a medical student who has completed his sophomore year at the University of Cincinnati will receive the Eugene B. Ferris, Jr., Memorial Award, consisting of a prize of \$150.00, together with an engraved scroll, symbolic of the award. The award will be made at the annual Medical College Convocation which is attended by faculty and students. The first award was made in September at the dedication ceremony for the new research wing of the Medical College. Simultaneously with the bestowing of the prize, a bronze plaque bearing a relief bust of Dr. Ferris was unveiled. In an area provided on the plaque, engraved plates bearing the names of the individual recipients of the award will be affixed.

Any additional funds which may remain after assurance of the perpetuation of the annual prize will be placed at the disposal of the Dean, to be used in sponsoring lectureships.

Dr. Ferris, at the time of his death in 1957, was a Regent of the American College of Physicians.

NORTH DAKOTA REGIONAL MEETING, A.C.P.

The Annual Regional Meeting of the American College of Physicians for North Dakota was held at Bismarck, September 12, 1959, under the Governorship of Dr. Lester E. Wold. Dr. H. Marvin Pollard, F.A.C.P., Ann Arbor, was the official representative of the Officers and Regents of the College. Dr. Pollard addressed the scientific session on "Steroid Therapy in Various Gastrointestinal Problems," and was the chief speaker at the banquet, his title being "The Responsibility of the American College of Physicians for Foreign Trainees."

The American Society of Internal Medicine for North Dakota and the North Dakota Heart Association held meetings in conjunction with the A.C.P. Regional Meeting.

GEORGE W. MERCK MEMORIAL LOAN FUND

A \$400,000 George W. Merck Memorial Loan Fund has been established by the Merck Company Foundation to provide financial aid to interns and residents. The Fund will assist deserving interns and residents to seek the best possible graduate training in teaching hospitals before entering practice. It is estimated that 60 to 100 doctors will benefit each year from the Fund.

The 18 medical schools participating are associated with the following universities: Boston, California, Chicago, Columbia, Cornell, Harvard, Illinois, Johns Hopkins, New York, Northwestern, Pennsylvania, St. Louis, Tufts, Vanderbilt, Vermont, Virginia, Washington (St. Louis), and Yale.

Graduates of other medical schools may also be eligible for loans if they take their internship or residency at any of the 48 teaching hospitals affiliated with the participating schools.

The Fund will give deserving graduates more freedom to select hospitals of their choice for internship, with less concern about the salaries to be received.

Administration of the Fund will be by the deans of the medical schools, who will have complete freedom in the selection of recipients, the amount of each loan, and the terms of repayment. Initial payments to the 18 schools have been completed, so that funds will be available from 1959 on.

THE TRUMAN G. SCHNABEL FUND

Dr. Truman G. Schnabel, F.A.C.P., has been honored by creation of a \$150,000 fund to aid worthy students at the University of Pennsylvania School of Medicine. Reflecting what he thought of his physician, Bertram C. Hopeman of Augusta County, Va., who died September 28, 1958, bequeathed this sum of money in memory of his wife and in honor of Dr. Schnabel, emeritus professor of medicine and former president of the Philadelphia County Medical Society.

Dr. Schnabel was a staff physician at Philadelphia General Hospital for 37 years, and Chairman of the American Board of Internal Medicine from 1949 to 1951.

Three generations of this medical family have practiced medicine in Pennsylvania. All are graduates of the University of Pennsylvania School of Medicine: Dr.

Schnabel in 1911, his father, Dr. Edwin D., in 1885, and his son, Truman G. Schnabel, Jr., F.A.C.P., in 1943.

Dr. John McK. Mitchell, dean of the school, in accepting the bequest said "... this fine bequest was in recognition of Mr. Hopeman's friendship, regard and affection for Dr. Schnabel. It comes at a very opportune time since medical students are badly in need of scholarship aid."

The Institute for Advancement of Medical Communication, New York, has been awarded a grant by the National Science Foundation for a study of "The Metabolism of New Scientific Information." The chief aim of this project is to investigate the processes by which new information resulting from cardiovascular and endocrine research becomes generally available to the scientific community. Richard H. Orr, M.D., Executive Director of the Institute, will serve as principal investigator.

BAHAMAS CONFERENCES

The Bahamas Conferences in Nassau in the Bahamas will be conducted on the following dates:

First Bahamas Allergy Conference, Nassau Beach Lodge, Nassau, Bahamas, March 5 until March 12, 1960;

Ninth Bahamas Medical Conference, British Colonial Hotel, Nassau, Bahamas, April 1 until April 14, 1960;

Post Convention Bahamas Conference, Nassau, Bahamas, June 18 until June 25, 1960;

Tenth Bahamas Medical Conference, British Colonial Hotel, Nassau, Bahamas, November 25 until December 16, 1960;

An official certificate of attendance will be issued to those taking part in the Conferences. Those attending may deduct, from their income tax returns, all expenses pertinent to the Conference.

There are no tropical illnesses in Nassau. The average temperature during the winter months is around 70°.

American and Canadian citizens do not require passports. Vaccination certificates are not now required.

There are direct flights to Nassau from Miami, Fort Lauderdale, New York and Toronto, and ships from New York and Miami.

For further information, please contact: Dr. B. L. Frank, Organizing Physician, Bahamas Conferences, P. O. Box 4037, Fort Lauderdale, Fla.

Personal Notes

At the opening of the Second World Conference on Medical Education, held in Chicago, August 29 to September 4, Dr. Raymond B. Allen, F.A.C.P., former Chancellor at the University of California at Los Angeles, commended the 1,500 educators from all over the world for coming to Chicago "to exchange experiences and ideas about the art of educating and training the physician."

Dr. Phil R. Manning, (Associate), Associate Dean and Director of the Post-graduate Division, University of Southern California School of Medicine, outlined a plan showing how organized medicine, representing the practicing physician and the medical schools, can work together in a mutually beneficial way for the good of all patients.

Dr. J. Wendell Macleod, F.A.C.P., Dean of Medicine, University of Sas-katchewan College of Medicine, Saskatoon, Canada, spoke on the "... overly technical

approach to the problems of the sick person."

Dr. Victor Johnson, F.A.C.P., Professor of Physiology, University of Minnesota (Mayo Foundation), told medical educators from 51 different countries that "Medicine is a struggle against nature for more knowledge, and nature loves to hide." In his presentation he mentioned that ". . . man's knowledge of the mechanism of disease has great gaps waiting to be filled in," and, for that reason, he urged physicians everywhere to become more interested in research early in their careers.

Dr. Richard H. Freyberg, F.A.C.P., Professor of Clinical Medicine, Cornell University Medical College, and Director of the Department of Rheumatic Diseases, Hospital for Special Surgery, New York City, delivered the Ninth Annual Pemberton Memorial Lecture before the Philadelphia County Medical Society on October 28, 1959. It dealt with the benefits, limitations and problems of the treatment of rheumatoid arthritis with corticosteroids, gold salts and salicylates; analysis of ten years study.

The lectureship is under the joint sponsorship of the Eastern Pennsylvania Chapter of the Arthritis and Rheumatism Foundation, the Philadelphia Rheumatism Society and the Arthritis Section of the Philadelphia County Medical Society.

The World Medical Association elected Dr. J. Renaud Lemieux, F.A.C.P., Quebec, Canada, as President of the organization for 1959–1960 at their 13th General Assembly held in Montreal, Canada, September 6–12, 1959.

Dr. Franz J. Ingelfinger, F.A.C.P., Boston, and Dr. Robert J. Vanderlinde, (Associate), Hanover, addressed the Joint Annual Meeting of the New Hampshire Medical Society and the Vermont State Medical Society held October 1–4 at Manchester-in-the-Mountains, Vt.

Dr. Chester Cassel, F.A.C.P., Miami, Fla., was a guest speaker at the 6th Annual Southeast Missouri Cancer Conference held at Cape Girardeau, October 4.

Dr. Joseph A. Wagner, F.A.C.P., Bryn Mawr, Pa., has been appointed Director of the Department of Medicine at Bryn Mawr Hospital, succeeding Dr. W. Wallace Dyer, F.A.C.P., Bryn Mawr, who resigned to accept the directorship of a new teaching division at the Philadelphia General Hospital.

Dr. John H. Talbott, F.A.C.P. (Ex-Governor for Western New York), served as a General Chairman at a Symposium on Developments in Hematology, held October 8 at the University of Buffalo School of Medicine.

Dr. William Dameshek, F.A.C.P., Boston, Dr. Leandro M. Tocantins, F.A.C.P., Philadelphia, and Col. William H. Crosby, Jr., (Associate), Medical Corps, U. S. Army, were participating speakers.

Dr. Walter B. Frommeyer, Jr., F.A.C.P., Birmingham, Ala., has been installed as President of the Alabama Heart Association. Dr. Frommeyer is Professor and Chairman of the Department of Medicine at the University of Alabama Medical Center.

Dr. Laurance W. Kinsell, F.A.C.P., Oakland, Calif., gave a lecture on "Metabolism of Fats" at the American Academy of Pediatrics Meeting, October 5-8, in Chicago.

Dr. Thomas Findley, F.A.C.P., Augusta, Ga., Dr. Leo J. Wade, F.A.C.P., New York, Dr. John G. Young, F.A.C.P., Dallas, and Dr. Carl Muschenheim, F.A.C.P., New York, addressed the 94th Annual Session of the Michigan State Medical Society at Grand Rapids, Mich., September 27-October 2, 1959.

Dr. Joseph H. Fries, F.A.C.P., Brooklyn, has been elected President-Elect of the New York Allergy Society.

The Henry G. Rudner, Sr., Award Paper, "The Acute Effects of Abdominal Paracentesis in Laennec's Cirrhosis upon Exchanges of Electrolytes and Water, Renal Function and Hemodynamics," was given by Dr. Martin E. Gordon, F.A.C.P., New Haven, Conn., at the 24th Annual Convention of the American College of Gastroenterology, held Sept. 21-23, at Los Angeles.

The New York Medical College, Flower and Fifth Avenue Hospitals, will sponsor a fifteen-day postgraduate cruise to the Caribbean. Dr. Linn J. Boyd, F.A.C.P., New York City, Director of the Division of Graduate Studies, has announced that the cruise will leave New York on February 25, 1960, and visit St. Thomas, La Guaira, Curacao, Cristobal, Kingston, and Havana, spending six days in these ports of call and nine days at sea.

The medical sessions will be held three hours each morning and during one afternoon while at sea. The faculty includes Drs. Kenneth R. Crispell, F.A.C.P., New York City, Director of Medicine, and David Scherf, F.A.C.P., New York City, Professor of Clinical Medicine (Cardiology).

Physicians may be accompanied by their wives.

Further information may be obtained from the Division of Graduate Studies, New York Medical College, Flower and Fifth Avenue Hospitals, Fifth Avenue at 106th Street, New York 29, N. Y.

Dr. William Nimeh, F.A.C.P., American University of Beirut, Beirut, Lebanon, has been elected President of the recently founded Lebanese Society of Gastroenterology.

Dr. Garfield G. Duncan, F.A.C.P., (Third Vice President of the College), Philadelphia, heads the Advisory Editorial Board recently established by the Army

Surgeon General's Office.

Other members of the Board are: Drs. Walter Bauer, F.A.C.P., Boston, Herrman L. Blumgart, F.A.C.P., Boston, Worth B. Daniels, F.A.C.P., Washington, D. C., Eugene C. Eppinger, F.A.C.P., Boston, Joseph M. Hayman, Jr., F.A.C.P., Boston, Yale Kneeland, F.A.C.P., New York City, Howard P. Lewis, F.A.C.P., Portland, Ore., (President of the College), Esmond R. Long, M.A.C.P., Pedlar Mills, Va., William S. Middleton, M.A.C.P., Washington, D. C., Donald M. Pillsbury, F.A.C.P. Philadelphia, Maurice C. Pincoffs, M.A.C.P., Baltimore, and Henry M. Thomas, Jr., F.A.C.P., Baltimore.

Serving ex officio, with others, on the Advisory Editorial Board is Col. Dan Crozier, (Associate), Chief Medical Consultant, Army Surgeon General's Office.

Dr. Stanley Greenhill, F.A.C.P., Edmonton, Alberta, Canada, has been appointed Professor of Social and Preventive Medicine, University of Alberta Faculty of Medicine.

At the Sixth Annual Meeting of the Academy of Psychosomatic Medicine, held in Cleveland during October, 1959, the following members of the College participated: Drs. Joseph B. Kirsner, F.A.C.P., Chicago; Charles H. Brown, F.A.C.P., Cleveland; M. Murray Peshkin, F.A.C.P., Milton Plotz, F.A.C.P., Felix Wroblewski, F.A.C.P., Burton Zohman, F.A.C.P., New York City; Edward Stainbrook, F.A.C.P., Los Angeles; Titus H. Harris, F.A.C.P., Galveston; Arthur R. Scherbel, F.A.C.P., Cleveland; Wilfred Dorfman, F.A.C.P., Brooklyn; Theodore Rothman, F.A.C.P., Los Angeles; and Victor Szyrynski, F.A.C.P., Ottawa.

Dr. Alvin Slipyan, F.A.C.P., Medical Research Director of Human Resources Corp., Albertson, N. Y., lectured on medical rehabilitation at the Government Hospital, Tel Hashomer, Israel, last July. On September 21, 1959, Dr. Slipyan was guest lecturer to supervisors and employees of the Mitchel Air Force Base, New York, on rehabilitation in industry.

Dr. Paul A. Van Pernis, F.A.C.P., Rockford, has been elected President of the Illinois Association of Blood Banks and Vice President of the Illinois Society of Pathologists.

Dr. Rafael Rodriguez-Molina, F.A.C.P., San Juan, Puerto Rico, gave a lecture on Schistosomiasis on September 1, 1959, at the monthly Medical Officers Scientific Meeting, Rodriguez U. S. Army Hospital, Fort Brooke, P. R.

Dr. John J. Kelly, Jr., (Associate), formerly Associate Professor of Medicine, State University of New York College of Medicine at New York City, is now Director of Medical Education and of Cardiology at Mercy Hospital, San Diego, Calif.

Dr. Thomas M. Durant, F.A.C.P., Philadelphia, Treasurer, was the official representative of the American College of Physicians at the President's Evening, September 28, 1959, in connection with the Forty-fifth Annual Clinical Congress of the American College of Surgeons at Atlantic City.

Dr. Claude Starr-Wright, F.A.C.P., Augusta, Ga., presented a paper at the 24th Annual Piedmont Post Graduate Clinical Assembly, Clemson, S. C., September 16-17, 1959.

Lt. Col. Harold E. Ratcliffe, (Associate), Wortham, Texas, has been promoted to the rank of Colonel. He has been chief of Walter Reed Army Hospital's Allergy Service since August, 1957.

Dr. John Lansbury, F.A.C.P., and Dr. Joseph L. Hollander, F.A.C.P., have been elected President and Vice President, respectively, of the Philadelphia Rheumatism Society.

Dr. Jacob C. Geiger, F.A.C.P., San Francisco, was recently a recipient of a "Distinguished Service" scroll presented by the Pan American Medical Association.

RESIDENCY REVIEW COMMITTEE IN INTERNAL MEDICINE

Dr. Howard Wakefield, F.A.C.P., Chicago, has not only been Chairman of the A.C.P. Residency Review Committee in Internal Medicine, but has been the overall Chairman of the Committee as a whole, working with the Council on Medical Education and Hospitals of the American Medical Association. He has now retired as Chairman of the overall Committee and Dr. Hugh R. Butt, F.A.C.P., Rochester, Minn., a member of the American Board of Internal Medicine, has succeeded him. Dr. Wakefield, however, remains Chairman of the A.C.P. Committee.

Dr. John C. Leonard, F.A.C.P., Hartford, a member of the College Committee, is the new Vice Chairman of the Committee as a whole. It is the policy of the Committee, consisting of representatives from the American College of Physicians and the American Board of Internal Medicine, to alternate the overall Chairman between the College and the Board.

In early September, Major General Oliver K. Niess, A.C.P. Governor, Surgeon General of the United States Air Force, addressed the physicians attending the first Advanced Course in Aerospace Medicine for Allied Medical Officers at the USAF School of Aviation Medicine, Brooks Air Force Base, San Antonio, Texas.

Dr. Roscoe L. Pullen, F.A.C.P., resigned as of August 31, 1959, as Dean of the University of Missouri School of Medicine and as Director of the University of Missouri Medical Center. Presently he is on leave of absence as Professor of Medicine at the University of Missouri, and is located at Spokane, Wash.

Dr. A. Carlton Ernstene, F.A.C.P., Cleveland, College Governor for Ohio, new President of the American Heart Association, addressed the Association's guests at their Annual Dinner in Philadelphia, October 25, 1959. The following members of the College presented papers at the Association's Scientific Sessions: Drs. Louis N. Katz, F.A.C.P., Chicago; Eugene A. Stead, Jr., F.A.C.P., Durham; Ernest Craige, F.A.C.P., Chapel Hill; and Irvine H. Page, F.A.C.P., Cleveland.

The Department of Medicine of the Menorah Medical Center, Kansas City, Mo., held its Annual A. Morris Ginsberg Memorial Seminar, November 4-5. The guest speaker was Dr. Morris Ziff, (Associate), Dallas, Professor of Medicine, Southwestern Medical School of the University of Texas.

Drs. Frank W. Davis, Jr., F.A.C.P., Robert E. Mason, F.A.C.P., and Martin L. Singewald, F.A.C.P., Instructors in Medicine at the Johns Hopkins University School of Medicine, Baltimore, were guest speakers at the Scientific Session of the West Virginia Heart Association's Annual Meeting at Martinsburg, W. Va., September 25, 1959.

Dr. Charles L. Leedham, F.A.C.P., Director of Education, Cleveland Clinic Foundation, was elected President of the American Therapeutic Society at its Annual Meeting at Atlantic City in June. Dr. Leedham, at the termination of his term of

office as Chairman of the Disaster Relief Committee of the Academy of Medicine of Cleveland, received a resolution of commendation from the City Council of Cleveland for his work in the civil defense effort.

Dr. John S. Gilson, F.A.C.P., Great Falls, Mont., was given a Grant from the Montana Heart Association for the purpose of bringing into stage of clinical usefulness several devices devised and developed so far by the Holter Research Foundation in Helena, Mont. These devices have as their purpose the recording of long periods of electrocardiographic tracings on tape and their rapid analysis. One of the devices utilizes a radio link, and another is a self-contained device worn by the patient. Both pulse patterns and electrocardiographic patterns can be analyzed by these devices, which may give a further dimension to pulse and electrocardiographic observations, which by these methods can be extended over a period of hours rather than minutes.

Recently George C. Griffith, F.A.C.P., Governor for Southern California, received a Distinguished Service Medallion of the Los Angeles County Heart Association on completing his term as President recently.

Dr. Griffith, Clinical Professor of Medicine at the University of Southern California School of Medicine, has made unique contributions to cardiovascular studies in Southern California. He has been a driving force in the development of the U.S.C. Cardiology section of the Los Angeles County Hospital, as well as other cardiac centers in Southern California.

He organized a formal one-year course in cardiology at the Los Angeles County Hospital in 1946. More than 100 physicians have taken this course.

Dr. Griffith is an active member of numerous societies. In addition to being Governor of A.C.P. for Southern California, he is a director and member of the policy committee of the American Heart Association, consultant to the Bureau of Rehabilitation and the Board of Public Health of the State of California. In 1959 he was elected a Fellow of New York Academy of Science.

Dr. Joseph Shaiken, F.A.C.P., Milwaukee, Wis., and Dr. Louis L. Perkel, F.A.C.P., Jersey City, N. J., were elected President and Secretary, respectively, of the American College of Gastroenterology at its annual meeting, September 20, 1959, in Los Angeles.

Dr. Victor Szyrynski, F.A.C.P., Professor of Psychotherapy and Associate Professor of Psychiatry, University of Ottawa, Canada, presented a paper on "Management of Frustration in Everyday Practice" before the Scientific Assembly of the Ohio Academy of General Practice in Columbus, Ohio, September 17, 1959.

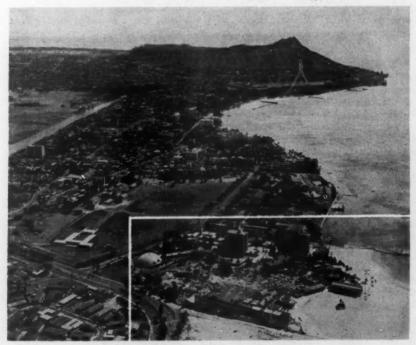
On his way back, he addressed the social workers of Metropolitan Toronto on "Psychological Dynamics of Marital Discord," September 21, 1959.

Dr. Nathaniel B. Kurnick, F.A.C.P., Associate Clinical Professor of Medicine, University of California School of Medicine at Los Angeles, participated in a working conference on the clinical aspects of radiation injury and the transplantation of bone marrow and other organs, held at the National Institutes of Health in Bethesda, Md. Dr. Kurnick reported on his experience with autologous bone marrow storage and reinfusion in patients treated with intensive radiotherapy and chemotherapeutic agents.

AMERICAN COLLEGE OF PHYSICIANS MEDICAL SEMINARS IN HAWAII

The Forty-first Annual Session of the College will be held in San Francisco, April 4-8, 1960. The next day, April 9, a Post-Convention group will fly from San Francisco by Pan-American Jet Clipper to Hawaii on a Post-Convention Tour under the management of Mr. Leon V. Arnold, 33 Washington Square, West, New York 11, N. Y.

The Jet Clipper will make the trip in five hours. The group will be greeted at the Honolulu Airport with flower leis, and will transfer to the Hawaiian Village Hotel—Village Tower or Ocean Tower. Many entertainment features have been



Airplane View of Honolulu and Diamond Head (with Hawaiian Village in rectangle).

arranged for the group throughout their stay. A special folder giving all the details has already been mailed to all members.

There will be a scientific program on Monday forenoon, April 11, a demonstration clinic on leprosy at Hale Mohalu; also a scientific program on Wednesday morning, April 13, at the Tripler Army Hospital. Dr. Hastings H. Walker, College Governor for Hawaii, and a group of the College Fellows will arrange the scientific program and act as hosts. A special folder covering the details of the scientific program will later be printed. Members participating in the scientific program are eligible to

deduct for themselves, not for their wives, a portion of their expenses that concern the scientific program and transportation.

Hawaii is exotic; the hotels are excellent; hospitality is unmatched; your comfort and convenience will be attended to in every detail by Mr. Arnold; the trip will be long-remembered. President and Mrs. Howard P. Lewis will head the party.

There are alternate plans for the return journey to the States. Those who desire may leave in the first contingent by Jet Clipper on Thursday, April 14, arriving in San Francisco on Friday, April 15. Another contingent may desire to remain for a three-day outer island tour—Maui and Hawaii. This group will leave Honolulu by plane on April 14 and will arrive back at San Francisco on April 17.



Hawaiian Village, Village Tower Hotel.

A view of the main gardens from across the Mirror Pond.

A third contingent may desire to remain in Honolulu until April 20, when they will sail on the S.S. Matsonia, arriving in San Francisco on the early morning of April 25.

For the first time in its history, the United States has drawn a group of islands into its midst as a State! And, during the first year of its statehood, the College will hold a meeting there. The Hawaiian group consists of eight islands and some scattered atolls. The four main islands are Oahu, on which Honolulu is located, Kauai, Maui and Hawaii, usually referred to as "The Big Island" because it is the largest of the group. The excursions cover the island of Oahu thoroughly and, with the extension, Maui and Hawaii.

Hawaii has modern cities and old plantation towns. It reveals small farms and taro fields but it also has multi-million dollar pineapple and sugar industries. It is sophisticated, naive, friendly, historical, modern—a mixture of countless religions, customs, races, cultures, ages, and yet it is thoroughly American. Our tour gives a comprehensive picture of the whole State.

The polyglot population of the islands includes Hawaiians, Japanese, Chinese, Koreans, Filipinos, Caucasians and others. This gives the islands their particular exotic flavor, their touch of many-worlds-in-one. This flavor and color has been incorporated into the tour by the various dinners and the Kodak Hula Show, which are all covered in the inclusive price.



THE OCEAN TOWER—A view of Waikiki's most distinguished resort hotel, fronting upon Waikiki's finest white sand beach. This building reflects the ultimate in Island living.

While Waikiki and Honolulu give Oahu a very definite charm for vistors, all the other islands attract and fulfill a variety of dream vacations, too. Hawaii Island combines Mauna Kea, highest island peak in the world, and Mauna Loa, still active volcano and largest mountain mass in the world, with the rich, lush, lazy village life of the Kona coast. Maui combines its Haleakala Crater, largest dormant volcano in the world, with the old whaling town of Lahaina.

The numerous outstanding features of Medical Seminars in Hawaii include jet planes for the round trip with five-hour service; optional return by ship; deluxe hotel rooms with lanais; complete sightseeing program of Oahu—five tours and three dinners with native entertainment; optional three-day Extension Tour to the Outer Islands, Maui and Hawaii; the whole tour set up with the Annual Meeting so that both require but two weeks away from the office anywhere in the United States, Canada and Mexico.



HULA SKIRT PLANS—Before any big festival, hula dancers are seen gathering ti-leaves to make their hula skirts. The ti plant grows as shown here. The girls split the leaf with their thumbs, and tie the leaves onto a stout cord—the cord goes around the waist, of course, and there you have the hula skirt, which will last about 4 weeks.—Hawaii Visitors Bureau.

It is urged that members and their friends and families make their reservations promptly. Options are limited. If you have mislaid the detailed itinerary sent you in November, write for another to Mr. Arnold, whose address appears earlier in this article. Many members of the College know Mr. Arnold very well through his former successful operations of post-convention tours for the College.

NEW ELECTIONS TO MEMBERSHIP IN THE AMERICAN COLLEGE OF PHYSICIANS

On November 14, 1959, the Board of Regents, on recommendation of the Committee on Credentials, provided for the following elections. Those listed in FULL CAPITALS were elected to Fellowship; those in lower case were elected to Associateship.

| Emanuel Abraham | Asbury Park, N. J. |
|---------------------------|--|
| Joseph Benjamin Aiken | |
| Leonard Clement Alexander | Detroit, Mich. |
| ANGELO PANAGEOTIS ANGE | LIDESPhiladelphia, Pa. |
| JOSEPH THOMAS AQUILINA | Buffalo, N. Y. (VA) |
| | Toronto, Ont., Canada |
| PERRY RICHARD AYRES | Columbus, Ohio |
| | The second secon |

| William H. Bachrach | Los Angeles Calif | |
|---|------------------------------|-------|
| William Thomas Bailey, Jr | | |
| | | |
| WILLIAM HENRY BAKER | | |
| Loren Call Barlow | | |
| Naseeb B. Baroody, Jr THOMAS MELVIN BATCHELOR | | |
| | | |
| Robert A. Baumler | | |
| Ernest Lovell Becker | | |
| William Horne Bennion , | Salt Lake City, Utan | |
| ERWIN EDWARD BENZIER | | |
| Kenneth George Berge | Kochester, Minn. | |
| Kenneth William Berger | | |
| Barnett Berman | | |
| STANLEY HERBERT BERNSTEIN | | |
| CARL ALFRED BERNTSEN, JR | | |
| CARLOS ENRIQUE BERTRAN | | |
| Morton Alvin Binder | St. Louis, Mo. | |
| WILLIAM HENRY BLAHD | | (VA) |
| Thomas Paul Blanshard | Claremont, Calif. | |
| Harold C. Blog | | |
| STANLEY THEODORE BLOOMFI | | |
| Morton David Bogdonoff | Durham, N. C. | |
| Galen Charles Boller | | |
| Martin V. Bonventre | | |
| ELI LEROY BORKON | | |
| Eugene George Boss, Jr | Springfield, Mass. | |
| HAROLD WILLIAM BOTTOMLEY | | |
| STANLEY EDWARD BRADLEY . | | |
| Gerald Myers Breneman | Birmingham, Mich. | |
| Leonard Breslaw | Beverly Hills, Calif. | |
| SAMUEL HENRY BRETHWAITE | Summit, N. J. | |
| James Curtis Broadbent | | |
| Robert James Brodrick | Montreal, Que., Canada | |
| Edward James Brotman | | |
| Bruce Larry Brown | | |
| HERBERT RUTHERFORD BROWN | N, JR Rochester, N. Y. | |
| KENNETH WILLIAM GORDON BI | ROWN Downsview, Ont., Canada | 0 103 |
| Walter Buckner, II | | |
| | | |

| Byron Hugh BuffSan Diego, Calif. |
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| Bernard Burack |
| William Eugene BurkhartColumbus, Ohio |
| MAURICE MADISON BURKHOLDER Boise, Idaho |
| Rowland Harvey Burns |
| THOMAS WADE BURNSColumbia, Mo. |
| MALCOLM BATES BURRISLakeland, Fla. |
| The second series of the serie |
| Clifford Roland CalleyTyler, Tex. |
| Guy Douglas CampbellJackson, Miss. (VA) |
| Peter D. Carras |
| Helen Ruth Cash |
| Charles Hilmon Castle |
| Charles Iams Cerney |
| John Orrin ChamberlainMilwaukee, Wis. |
| David Labe Chamovitz |
| BRUCE FREDERICK CHANDLERM.C., U. S. Army |
| Max Earl Chervin |
| Anna Marie Chirico |
| |
| Bernard Chojnacki |
| Lawrence Granam Unristianson |
| Joaquin Gonzales Cigarroa, Jr Laredo, Tex. |
| Yale Citrin |
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| Leighton Eggertsen CluffLutherville, Md. |
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| Walter Lee Evans | .New York, N. Y. |

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| Stanley Farber | |
| Kevin John Fay | |
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| James Flexner | |
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| John Graham Gillis | Vancouver, B.C., Canada |
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| WILLIAM HENRY GLASS | |
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| Robert Levine | |
| Saul Charles Levine | |
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| Gerald Lieberman | |
| Tung Kuang Lin | |
| Sherman Brance Lindsey | |
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| John Hoover Moon |
| John C. MooreLos Angeles, Calif. |
| Victor Augustus Moore |
| Gerald E. MuehsamOrange, N. J. |
| ALEXANDER ADO MUELLERLos Angeles, Calif. |
| Frederick Rolla Mugler, JrSan Luis Obispo, Calif. |
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| PAUL ANDREW NELSON | . Lakeville, Conn. |
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| Elmer Pader SAMUEL WATSON PAGE, JR. FITZHUGH CARTER PANNILL, JR. SOLOMON PAPPER JOHN LAWRENCE PARNELL Orest Joseph Parrillo William Belle Parsons, Jr. Robert Thayer Patey Francis Marion Pearce, Jr. H. ROWLAND PEARSALL William Hale Perkins SEYMOUR MONROE PERRY William David Perry Robert Joseph Peters VOL KEENEY PHILIPS Leonard Vernon Phillips Arthur Stanwood Pier, Jr. Ben Pinsky James Allen Pittman, Jr. Donald G. Pocock MARK MOSES POMARANC | Miami, Fla. Corsicana, Tex. Waban, Mass. (VA) Vancouver, B. C., Canada Omaha, Nebr. (VA) Madison, Wis. Springfield, Ill. Austin, Tex. Seattle, Wash. Little Rock, Ark. (VA) Los Angeles, Calif. St. Louis, Mo. Masontown, Pa. Columbus, Ohio Akron, Ohio Boston, Mass. Culver City, Calif. Birmingham, Ala. (VA) Massillon, Ohio |
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| Arthur U. Rivin | Los Angeles, Calif. |

| Edward D. Robbins | San Francisco, Calif. |
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| Llewellyn Nicholson Roberts | Victoria, B. C., Canada |
| Theodore Rodman | Philadelphia, Pa. (VA) |
| Hector F. Rodriguez-Estape | Ponce P R |
| Paul Carl Roock | Santa Ana Calif |
| David Mayer Roseman | New York N V |
| WILLIAM HAROLD ROSENBLATT | Jackson Miss |
| RICHARD STARR ROSS | |
| Leon Morton Rothman | |
| Donald Eugene Rowley | Ashal Mass |
| Albert Trains Debugger | Chicago III |
| Albert Irving Rubenstone | Austin Ton |
| JOHN WILLIAM RUNYAN, JR | Austin, Tex. |
| JOHN WILLIAM KUNYAN, JR | Albany, N. X. |
| HERMAN DAVID RUSKIN | Rockville Centre, N. Y. |
| IAN EDWIN LAWMAN RUSTED | St. John's, Nfid., Canada |
| Bernard Anatole Sachs | New Vort N V |
| John Smyth Salatich | |
| Santiago A. Sanchez | |
| Douglas Woodford Sanders | Almon Ohio |
| Alois McKeon Scheidel | Manhata Minn |
| JOSEPH EDWIN SCHENTHAL | Mankato, Minn. |
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| Eugene Joseph Scherba | Perena, Mont. |
| Francis Edward Schlueter | Pasadena, Calif. |
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| Albert William Schreiner | Cincinnati, Ohio (VA) |
| Carlyle William Schumacher | Short Hills, N. J. |
| Irving Schwartz | Livingston, N. J. |
| Morris Jacob Seide | West Hartford, Conn. |
| Carlton Lasley Sexton | |
| Joseph Morris Shachtman | |
| HORACE MELVIN SHAFFER | |
| NORMAN SHAFTEL | |
| John Rush Shanahan | Newtown Square, Pa. |
| Henry Melvin Shanoff | Toronto, Ont., Canada |
| Richard P. Shapera | Pittsburgh, Pa. |
| John Blasdel Shapleigh, 2nd | St. Louis, Mo. |
| VICTOR JOSEPH HOUSTON SHARPE | |
| SOL SHERRY | St. Louis, Mo. |
| Jack William Shields | Chicago, Ill. |
| MILTON SHOSHKES | Newark, N. J. |
| ALBERT MYRON SILVER | Newark, N. J. |
| Mervin Clark Silverthorne | Denton, Tex. |
| Charles Franklyn Sims | New York, N. Y. |
| Manuel Sklar | Detroit, Mich. |
| Edwin Lindale Smith | |
| GEORGE PAUL SMITH | |
| Charles Allen Smolt | Ventura, Calif. |
| Bernard Herbert Smookler | |
| Cheves McCord Smythe | Charleston, S. C. |
| Thomas Henry Snider | Monroe, Mich. (VA) |
| Norman Sollod | Columbia, S. C. (VA) |
| Samuel D. Solway | Toronto, Ont., Canada |
| | |

| He Jeas SA Lee Door ST Noo Free John Jos Irw Cha Wi Ric Daw Jam Roh | e J. Sosman nry David Specht m Aileen Spencer MUEL SPINNER MUEL SPINNER Myrl Spivey nald Julian Stallard ANLEY STARK rman Stanley Stearns meman Irby Stephens m Amos Stephens m Amos Stephens m Amos Stephens m Arnos S | Glendale, Calif. Chicago, Ill. New Haven, Conn. West Palm Beach, Fla. St. Joseph, Mo. Brooklyn, N. Y. West Newton, Mass. Asheville, N. C. Jacksonville, Fla. Nahant, Mass. Elkins Park, Pa. Galveston, Tex. Chattanooga, Tenn. Miami, Fla. Santa Fe, N. M. Dallas, Tex. Wausau, Wis. Douglaston, L. I., N. Y. |
|---|--|---|
| Joh | n Easter Sweeney | Topeka, Kans. |
| Sidi JAI Eug Dar E. San ER: Wa Her MO Will RO. WA Lou WII | ney H. Tabor MES TATSUO TAGUCHI gene Max Teich niel Jacob Tenenberg CLINTON TEXTER, JR. n Harold Thal NEST OTTO THEILEN lter Herman Thiede nry Duke Thomas PRRIS EDWARD THOMAS liam H. Thomas BERT GLENN THOMPSON LATER SIMEON THOMPSON, JR. nis Tobian, Jr. LLIAM HENRY TODD | East Rockaway, N. Y. Dayton, Ohio (VA) Huntington, N. Y. Boston, Mass. (USPHS) Chicago, Ill. Oakland, Calif. (VA) Iowa City, Iowa Milwaukee, Wis. Birmingham, Ala. Indianapolis, Ind. San Francisco, Calif. M. C., U. S. Army Los Angeles, Calif. Minneapolis, Minn. Long Beach, Calif. |
| Rob | ert Upson | Cleveland, Ohio |
| WII | LLIAM NEWTON VALENTINE | Pacific Palisades, Calif. Flourtown, Pa. |
| Will JAM Alex STA Will Edg FRA Max NEI | liand John Wagner liam Paul Wagner MES HARDIN WALL kander Wallace, III ANLEY LAWRENCE WALLACE liam James Walsh ar Humes Ward ANK PELOUZE WARD to Harry Weil LSON JURIS WEISER NJAMIN BOISSEAU WEISIGER, III | Port Washington, N. Y. White Plains, N. Y. Los Angeles, Calif. Brooklyn, N. Y. Hamilton, Ont., Canada Erie, Pa. Lumberton, N. C. Los Angeles, Calif. Wilkes-Barre, Pa. (VA) |

| MARK STILES WELLINGTON | Framingham, Mass. |
|---------------------------|----------------------|
| WILLIAM CHARLES WERMUTH | Philadelphia, Pa. |
| RICHARD NUTTER WESTCOTT | East Cleveland, Ohio |
| Jefferson Earle White, Jr | |
| John Marshall Wilkinson | |
| Gerald Albert Williams | |
| Stewart McGehee Williams | |
| JESSE RODMAN WILSON, JR | |
| Herbert Lee Wineland | |
| THOMAS ADAMS WITTEN | |
| James Clifton Wright, Jr | |
| Eugene Myron Wyso | |
| Harry Robert Yates, Jr | Roanoke, Va. |
| CEORCE WILDIN ZELLIEF | Harrison Ton |
| GEORGE WILBUR ZELUFF | |
| WILLARD JACK ZINN | Albambra Calif |

OBITUARIES

The College records with sorrow the deaths of the following members. Their obituaries will appear later in these columns.

Delbert M. Bergenstal, M.D., F.A.C.P., Bethesda, Md. Herbert T. Brooks, M.D., F.A.C.P., San Marino, Calif., June 29, 1959 William T. DeSautelle, M.D., F.A.C.P., Knoxville, Tenn., August 9, 1959 C. J. Fishman, M.D., F.A.C.P., Oklahoma City, Okla., July 26, 1959 Robert H. Hackler, Jr., M.D., F.A.C.P., Washington, D. C., Aug. 4, 1959 Ralph Horton, M.D., F.A.C.P., Oneonta, N. Y., September 17, 1959 Dunne W. Kirby, F.A.C.P., Captain, (MC), U. S. Navy, Sept. 7, 1959 Eillis Lamb, M.D., F.A.C.P., Clinton, Okla., June 14, 1959 Estella G. Norman, M.D., F.A.C.P., Davis City, Iowa Leon Rosove, M.D., F.A.C.P., Los Angeles, Calif., Aug. 11, 1959 Wallace W. Ryall, M.D., (Associate), Youngstown, Ohio, April 25, 1959 Porter P. Vinson, M.D., F.A.C.P., Richmond, Va., Aug. 28, 1959

DR. JOHN PERCY ANDERSON

John Percy Anderson, internist and cardiologist, died in Cleveland, Ohio on September 5, 1959 of metastatic carcinoma of the colon. He was born in Wilsonville, Ontario in 1897 and received his undergraduate and medical education from the University of Toronto. After graduating in 1920, he served a two-year internship and residency at Toronto General Hospital and then spent a year as staff physician at Calydor Sanatorium in Muskoka, Ontario. In 1923 he joined the staff of the Cleveland Clinic and continued in this capacity until he entered private practice in Cleveland in 1931. At the time of his death he was Director of Medicine of the Euclid-Glenville Hospital and Senior Medical Consultant at St. Vincent Charity Hospital.

Dr. Anderson was a member of the American Medical Association, Ohio State Medical Association, Academy of Medicine of Cleveland, American Heart Association, and the Interurban Clinical Club. He became a Fellow of the American College of Physicians in 1927 and was a Diplomate of the American Board of Internal Medicine.

Dr. Anderson was a skillful, sincere and highly admired physician and will be greatly missed by his colleagues and his patients. He is survived by his wife, Mrs. Marion McEwen Anderson, 30575 Brookwood Drive, Pepper Pike 24, Ohio, a daughter and a son. To them, the Officers and Fellows of the College extend their heartfelt sympathy.

A. CARLTON ERNSTENE, M.D., F.A.C.P., Governor for Ohio

DR. OSCAR BERGHAUSEN

Dr. Oscar Berghausen died in the Good Samaritan Hospital, Cincinnati, Ohio on July 27, 1959, following a heart attack. He was 80 years of age. His undergraduate education was obtained at the University of Cincinnati where he majored in chemistry, and he received his medical degree from the Medical College of Ohio in 1904. After a year's internship at the Cincinnati General Hospital, he pursued postgraduate training abroad for two years. During this time, he studied at the University of Berlin under Emil Fischer and Abderhalden, and later at the Institute of Infectious Diseases under Wassermann. He then spent six months at the University of Munich and studied later at St. Mary's Hospital, London, in the laboratory of Sir Almroth Wright. On his return to Cincinnati he opened his office for the practice of internal medicine and maintained this office until a few months before his death.

Dr. Berghausen was the founder of the first serological laboratory in Cincinnati and was its director from 1910 until 1931. From 1912 until 1928 he was assistant professor of medicine at the Medical College of Ohio (University of Cincinnati College of Medicine), and at various times he was also pathologist to the Christ, Good

Samaritan and Bethesda Hospitals of Cincinnati.

Dr. Berghausen was a member of the American Medical Association and the Ohio State Medical Association. He was a Diplomate of the American Board of Internal Medicine. He became a Fellow of the College in 1923, and a life member in 1934. He was one of four physicians who founded the American Society of Bacteriologists and was at one time President of the Cincinnati Medical Research Society.

Dr. Berghausen contributed extensively to medical literature on the subjects of clinical pathology, immunology, allergy, and the various anemias. He also contributed much to studies in metabolism, the early diagnosis and treatment of syphilis, and specific diagnostic tests for tuberculosis. His bibliography included over 75

medical papers.

Dr. Berghausen was revered as a scholarly physician and was held in highest esteem by his colleagues. He is survived by his widow, 11 Belsaw Place, Cincinnati 20, and by two sons and a daughter.

JACOB L. TUECHTER, M.D., F.A.C.P.

DR. EDWARD WELLES BIXBY

Dr. Edward Welles Bixby, F.A.C.P., Glen Summit Springs, Mountain Top, Pennsylvania, died August 21, 1959, at the age of 74.

Born in Wilkes-Barre, Pennsylvania, he graduated from Princeton University in 1907, and received his M.D. degree from the School of Medicine, University of Pennsylvania, in 1911. Following an internship in the Pennsylvania Hospital, Philadelphia, he served as Resident in Pathology in the same institution, 1913–1914.

During World War I he attained the rank of Lt. Colonel, MC. Subsequently he served as Internist, Medical Advisory Board 5, Pennsylvania Selective Service. His staff appointments included: Chief of the Medical Service, Wilkes-Barre General Hospital, and Visiting Physician, White Haven Sanatorium.

Active in civic and medical organizations, his services included membership on the Pneumonia Control Commission, Pennsylvania State Medical Association; and President, in 1934, of the Luzerne County Medical Society. He was elected to Fellowship in the American College of Physicians in 1938, and became a Life Member in 1944

Dr. Bixby was beloved by his patients and colleagues, setting a fine example for both. He made a substantial contribution to medicine in his community. He is survived by his wife, and son, Dr. Edward W. Bixby, Jr., of Philadelphia.

WILLIAM A. JEFFERS, M.D., F.A.C.P., Governor for Eastern Pennsylvania

DR. ERNEST MOORE FISHER

Dr. Ernest Moore Fisher, 84, of Washington, D. C., died May 31, 1959, at Baker Memorial Division, Massachusetts General Hospital, Boston, Massachusetts, after an illness of seven months.

A naturalized U. S. citizen, he was born November 20, 1875, in Crewe, England, and educated privately until he entered medical school. He received his M.D.-C.M. degree from the Medical Faculty of McGill University, Montreal, Canada, in 1904. He was licensed to practice in Maine in 1904 and in New Jersey in 1909. He served at both the Worcester State Hospital, Worcester, Massachusetts, and the New Jersey State Hospital at Morris Plains.

He was clinical assistant and instructor at the New York Postgraduate Medical School and Hospital from 1909 to 1913, and was the neuropsychiatric examiner for county boards in New Jersey fro m1913 to 1918. He was elected a Fellow of the American College of Physicians in 1918 and became a Life Member in 1934.

Dr. Fisher served as a Captain in the Army Medical Corps in World War I and then became a member of the U. S. Public Health Service for five years. In 1924, he joined the Veterans Administration in its claims and appellate divisions specializing in evaluation of psychiatric disabilities. In 1935, he became a consultant to the Veterans Administration Board of Veterans Appeals.

He was a Diplomate on the American Board of Psychiatry and Neurology. He was also a Member of the New Jersey Medical Society, Lehigh Valley Medical Association, American Medical Psychological Association, Morris County (N. J.) Medical Association, and the British Medical Association.

Dr. Fisher was probably the Government's oldest full-time professional employee. When he reached the compulsory age limit for retirement of 70 years, he was granted a special indefinite extension of his appointment by the White House and he continued actively on duty until a few weeks before his death.

Dr. Fisher is survived by a nephew, Dr. Trenholm L. Fisher, of Ottawa, Ontario, Canada.

WILLIAM S. MIDDLETON, M.D., M.A.C.P., Governor for Veterans Administration

DR. GEORGE HOWARD GEHRMANN

Dr. George Howard Gehrmann died September 3, 1959, at the age of 68. From 1926 until 1955 he had served as Medical Director, E. I. duPont de Nemours and Company, Wilmington, Delaware.

Dr. Gehrmann was born in Norwalk, Connecticut, October 11, 1890. He received his medical education in the Long Island Medical College. In addition to his

work in occupational medicine he found time to serve as Assistant Professor of Preventive Medicine (1939), the Medical College of Virginia, Richmond.

Dr. Gehrmann was responsible for a most progressive program in his organization, encompassing toxicology, experimental medicine, and the care of employees. A consultation-type examination, in keeping with high standards of internal medicine, was available for all personnel. Under his guidance a highly effective regimen for the correction of alcoholism was put into effect.

For his part in the development of industrial medicine he was awarded, in 1955, the William S. Knudsen Award of the Industrial Medical Association. In the same year the American Academy of Occupational Medicine established the George H. Gehrmann Lectureship in his honor.

Dr. Gehrmann was the author of a number of scientific reports. The College records with deep regret the passing of an outstanding Fellow. He is survived by Mrs. Gehrmann, Chadds Ford, Pennsylvania.

WILLIAM A. JEFFERS, M.D., A.C.P. Governor for Eastern Pennsylvania

DR. HAROLD WALTER JONES

Harold W. Jones, M.D., F.A.C.P., was found dead in his office in the Aldine Trust Building in Philadelphia on September 1, 1959. An autopsy disclosed that he died of coronary artery disease.

Dr. Jones was born in Newark, N. J., on February 1, 1891, attended the Peddie Institute in Hightstown, N. J., and graduated from Jefferson Medical College in 1917. In 1943 he received an honorary Doctor of Science degree from Villanova College. Following his graduation Dr. Jones interned at Jefferson Hospital for one year and then served as Chief Resident Physician for two years. Between his internship year and his chief residency, Dr. Jones served as a Captain in the Army Medical Corps during World War I and was stationed as an instructor in the School of Military Medicine at Ft. Oglethorpe, Georgia. He was associated in a teaching capacity with Jefferson Medical College for forty years before he retired in 1957 when he was made Emeritus Professor of Clinical Medicine.

Early in his career Dr. Jones became closely associated with Dr. Thomas McCrae, then the Magee Professor of Medicine and Head of the Department at Jefferson. Dr. Jones was among the first to apply extensively the tecimic of direct transfusion of blood and was responsible for the first observations of the effect of blood transfusions in many clinical states. He introduced several refinements in the methods of transfusing blood directly, and achieved a high degree of skill in carrying out this procedure. Dr. Jones participated in the activities of the Association of American Physicians, and presented many papers, most of them dealing with disorders of the blood, before that Association. He was responsible to a large extent for bringing to Jefferson Medical College a sizable bequest from the Cardeza estate, principally because of his close relationship with Mr. and Mrs. Thomas Cardeza of Philadelphia. As a result of his efforts the Charlotte Drake Cardeza Foundation for Hematological Research was organized.

Dr. Jones was an energetic, devoted physician who commanded a wide circle of friends. He was a Diplomate of the American Board of Internal Medicine and a member of the Interurban Clinical Club, the Association of American Physicians, The Philadelphia College of Physicians, the American Medical Association and of many local groups.

Dr. Jones is survived by his wife, the former Elizabeth Hughes Farquhar, whom he married in 1925, and a daughter, Mrs. Patricia Lewis.

LEANDRO M. TOCANTINS, M.D., and WILLIAM A. JEFFERS, M.D., Governor for Eastern Pennsylvania

DR. ROBERT FRANCIS MILLER

On July 11, 1959, the medical career of Robert Francis Miller was prematurely ended when he died, at the age of 50, of carcinomatosis,

Dr. Miller was born in Victoria, B. C., on July 5, 1909, and spent his early childhood in this Canadian city. Later he moved to Aberdeen, Washington. After graduation from high school in Aberdeen, he attended the University of Oregon, in Eugene, and there received his Bachelor of Arts degree in 1932. Three years later, in 1935, the University of Oregon Medical School conferred on him the degree of Doctor of Medicine.

Dr. Miller took his internship at the Multnomah County Hospital in Portland. Subsequently he held a preceptorship in the offices of Drs. T. Homer Coffen, Homer P. Rush, and Ernest L. Boylen. Specializing in internal medicine, Dr. Miller's primary interest lay in diseases of the cardiovascular system.

During World War II, Dr. Miller was Ward Officer and Chief of the Cardiovascular Service of the 46th General Hospital of the United States Army. With the hospital from 1942 to 1945, Dr. Miller served eighteen months of that time in the United States and two years in Africa and France. After his separation from the Service, with the rank of Major, in the spring of 1946, Dr. Miller resumed his practice in Portland.

From 1937 to 1942 Dr. Miller was a clinical instructor in the Department of Medicine (Outpatient Clinic) of the University of Oregon Medical School. Resuming his teaching duties in the same school in 1946 on his return from the war, he was appointed a Clinical Associate in Medicine. In this capacity he served until his death.

Dr. Miller was on the active staff of St. Vincent Hospital. He was on the associate staff of Providence Hospital,

While still in medical school, Dr. Miller was elected to Alpha Omega Alpha. He was a Diplomate of the American Board of Internal Medicine and an Associate in the American College of Physicians since 1948. He held membership in the American Medical Association, the Multnomah County Medical Society, the Oregon State Medical Society, the North Pacific Society of Internal Medicine, and the American Federation for Clinical Research.

Dr. Miller is survived by his wife Judy and their three sons, Tomas, James and John, who live in the family home at 1010 S. W. Westwood Court in Portland. Also surviving Dr. Miller is a brother, Kenneth, of Portland, and a sister, Mrs. Robert J. Hepburn, of Nanaimo, B. C.

MERL L. MARGASON, M.D., Governor for Oregon

DR. LEANDER ARMISTEAD RIELY

Dr. Riely was born September 14, 1874, in New Albany, Indiana. He graduated from Hanover College with an A.B. degree in 1895, and received his A.M. degree from the same school in 1899. Dr. Riely received his M.D. degree from the University of Louisville School of Medicine in 1898. He interned for one year in Louisville, and moved to Oklahoma City on May 10, 1899 to begin the practice of medicine.

Dr. Riely assisted in founding the Epworth College of Medicine in 1903. This later became the Oklahoma University Medical School and Dr. Riely became a member of its first medical faculty.

As a faculty member, Dr. Riely taught normal histology, bacteriology, and pathology. It has been stated that these subjects were assigned to him purposely because he owned the only microscope in Oklahoma City. Dr. Riely retained the rank of professor throughout his teaching career until he became Emeritus Professor of Medicine in 1946.

Dr. Riely took postgraduate work both in this country and abroad and was an instructor in the School of Military Medicine at Fort Oglethorpe, Georgia during World War I. Thereafter, he became a Lieutenant Colonel (inactive) in the Medical Reserve Corps of the U. S. Army.

Dr. Riely was a member of the American Medical Association, the Medical Society of the Southwest, the Southern Medical Society, the Oklahoma State Medical Society, the Oklahoma County Medical Society, the Academy of Medicine of Oklahoma City and the University of Oklahoma Clinical Society. He became a Fellow of the American College of Physicians in 1920 and served the College as Governor for Oklahoma from 1927 to 1946.

On January 11, 1905, Dr. Riely married Miss Gertrude Elizabeth Dorrell, who survives him, and who lives at 1 Brooks Road, New Canaan, Connecticut.

As a physician, Dr. Riely was an outstanding success. He had a fundamental knowledge of medicine coupled with real diagnostic acuity, human understanding and gentleness. He had a genuine Scottish sense of humor which made him tremendously popular with his students and colleagues alike. Dr. Riely's passing will leave many saddened friends, former students and colleagues throughout the United States.

JOHN C. LEONARD, M.D., Governor for Connecticut

DR. LEONARD GEORGE ROUNTREE

Dr. Leonard George Rountree of Miami Beach, Florida, died June 2, 1959 after a lingering illness. He was born April 10, 1883, in London, Ontario, Canada.

He received his M.D. Degree from the University of Western Ontario Medical College in 1905, and an Sc.D. (Honorary) from the University of Western Ontario in 1916.

He had a very distinguished career. He was Associate Professor of Medicine at Johns Hopkins University, 1914-1916. He was Medical Chief, University Hospital (Minneapolis), 1916-1920. He served in the Army Medical Corps in 1918 and he was one of two men primarily responsible for establishing our first Military Department of Aviation Medicine. He was Chief of the Division of Medicine, Mcyo Clinic and Foundation, 1920-1928. He was a member of the Advisory Council of he Biochemical Research Foundation, Newark, Delaware in 1932. About 1932 he became Director of the Philadelphia Institute of Medical Research. He was Research Clinician of the Philadelphia General and Presbyterian Hospitals; Vice-Chairman of the National Committee on Mental Health; he was a Trustee of London (Canada) Association for War Research. In 1940 he received a Presidential Appointment as Chief of the Medical Division of the United States Selective Service, Washington, D. C. He was Chairman of the Dean's Committee and Chief Consultant of the Veterans Administration Hospital of Coral Gables, Florida, at which time he became a resident of Dade County. This was about 1945. He was Chairman of the Medical Advisory Board and Chief Consultant to the American Legion from 1944 to 1954. He was a Diplomate of the American Board of Medicine and he was a Fellow of the American College of Physicians from 1928.

He was a member of the American Medical Association (Chairman of Section, 1920); a member of the Mental Health Society of South-Eastern Florida; The American Society for Clinical Investigation; The American Society for Advancement of Science; The Dade County Medical Association of Florida, and The Association of American Physicians.

After moving to Miami he became interested in the idea of assisting and creating the Medical School at the Miami University of Miami, Florida. He secured from the Veterans Administration the loan of a vacant building which has housed the Medical School from its early beginning.

Dr. Rountree will be missed by his many associates and friends.

KARL HANSON, M.D.

DR. ARTHUR HAWLEY SANFORD

Dr. Arthur Hawley Sanford, head of the Section of Clinical Pathology of the Mayo Clinic from 1911 to 1946, and emeritus professor of clinical pathology in the Mayo Foundation, Graduate School, University of Minnesota, died at his home in Rochester, Minnesota, on April 28, 1959, of coronary insufficiency.

Dr. Sanford was born in New Albin, Iowa, on January 12, 1882, the son of Amanda Elizabeth Gilbert Sanford and Alcimore Mead Sanford. He enrolled as a student at Northwestern University, from which he received the degree of Bachelor of Arts in 1904, and the degrees of Master of Arts in physiology and Doctor of Medicine in 1907. From 1907 to 1911 he was a member of the faculty of medicine at Marquette University, where he was successively assistant professor, associate professor and professor of physiology.

When the Mayo Foundation was established in 1915 Dr. Sanford was appointed an associate professor of clinical pathology and parasitology. He was advanced to professor in 1921, and he held this chair until 1950. He became a senior consultant of the Mayo Clinic in 1946, and retired from the Mayo Clinic in 1949.

Dr. Sanford soon became widely known in the field of clinical pathology, for he made many contributions to it. He was a co-author, with the late Dr. James C. Todd, of *Clinical Diagnosis by Laboratory Methods*, a standard text in the field.

Dr. Sanford was a fellow of the American College of Physicians and a member of the Minnesota State Medical Association (which elected him to the 50-year club in 1957), the American Medical Association, the American Association for the Advancement of Science, the American Society of Immunologists, the Society for Experimental Biology and Medicine, the Alumni Association of the Mayo Foundation, the Society of the Sigma Xi, the Alpha Omega Alpha medical honor society, the Alpha Kappa Kappa professional medical fraternity and the Sigma Nu academic fraternity. He was a member and had been a steward of the Methodist Episcopal Church. He was also a 32nd degree Mason (Scottish Rite) and a Knight Templar (York Rite).

Dr. Sanford is survived by his wife Margaret.

HUGH R. BUTT, M.D., Governor for Minnesota

DR. WILLIAM RICHARD SULMAN

Dr. William Richard Sulman, F.A.C.P., died April 24, 1959, at the age of 60. Born in Reading, Pennsylvania, he attended the University of Pennsylvania, then received his M.D. degree in 1925 from the University of Maryland.

Following an internship in the York General Hospital, York, Pennsylvania, he pursued postgraduate study in cardiology, 1937–1941; and in clinical pathology, and radiology, 1941–1943. He served as Chief of Medicine and Chief of Cardiology,

St. Joseph's Hospital, Hazleton, Pennsylvania. In the Hazleton State Hospital he was Associate Chief of Medicine, and an Instructor in Medicine and Cardiology in the School of Nursing.

Dr. Sulman was elected to Fellowship in the American College of Physicians in 1951. In addition to holding memberships in county, state, and national medical societies he was also a member of the American Heart Association, a Fellow of the American College of Cardiology, and a Diplomate of the American Board of Internal Medicine.

His colleagues join Mrs. Sulman, 81 North Laurel Street, Hazleton, Pennsylvania, and two sons, in sharing a deep sense of loss at this time.

WILLIAM A. JEFFERS, M.D., F.A.C.P., Governor for Eastern Pennsylvania

DR. CLYDE ALBERT UNDINE

Dr. Clyde A. Undine was born in Minneapolis, Minnesota, in 1886 and died on August 20, 1959.

Dr. Undine attended the University of Nebraska where he received the degree of Bachelor of Science. In 1916 he received the degree of Doctor of Medicine from the University of Nebraska College of Medicine. His postgraduate training was done at Tulane University, Columbia University, Omaha-Midwest, and Cook County Hospital in Chicago.

He was a pathologist at Ashburg Hospital, Assistant Physician at the Swedish Hospital, and was a member of the staff at St. Barnabas, St. Andrews, and Lutheran Deaconess Flome and Hospitals. He was a member of the Minnesota Department of Health and an Instructor for the American Red Cross.

Dr. Undine was a member of the American Medical Association and of the Minnesota State Medical Society. He had been an associate member of the American College of Physicians since 1926.

He is survived by his wife, Effi D. Undine.

Hugh R. Butt, M.D., Governor for Minnesota

DR. HENRY WOLFER

Dr. Henry Wolfer was born in 1885 in New York City and died on May 23, 1959 in Monterey, Massachusetts.

Dr. Wolfer received his M.D. Degree at Bellevue Medical College in 1908.

From 1942 to 1944 he was Clinical Professor of Medicine, Long Island College of Medicine in Brooklyn. In addition, he served as Consulting Physician, King's County Hospital, Long Island Medical College, and at Mary Immaculate (Jamaica) and Swedish Hospitals.

He was a member of the American Medical Association, New York State Medical Society, King's County Medical Society, Brooklyn Society of Internal Medicine, Eastern Medical Society and the Brooklyn Pathological Society. He was elected to Fellowship in the American College of Physicians in 1920 and later became a Diplomate of the American Board of Internal Medicine.

His publications included "Treatment of Tuberculous Ulcer of the Tongue with Streptomycin" in 1948, and "Coronary Disease in Women" in 1949.

Dr. Wolfer is survived by his son, Henry George Wolfer, Monterey, Massachusetts. It is with sincere regret his death is recorded.

E. Hugh Luckey, M.D., Governor for Eastern New York

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1960—San Francisco, Calif., April 4–8

1961—Bal Harbour, Fla., May 8-12

1962—Philadelphia, Pa., April 9–13

1963—Denver, Colorado, April 1-5

1964—Atlantic City, New Jersey, April 6-10

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1959 Supplement, Cumulative Index to Annals of Internal Medicine—

The Cumulative Index to Vols. 1–40 was published in 1955. Supplements are published every five years. The current Supplement, Vols. 41–50, covering the intervening years, June, 1954, through June, 1959, will be ready for delivery during January, 1960.

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- 2. Bellet, S.: Amer. Heart J. 56:479, 1958.
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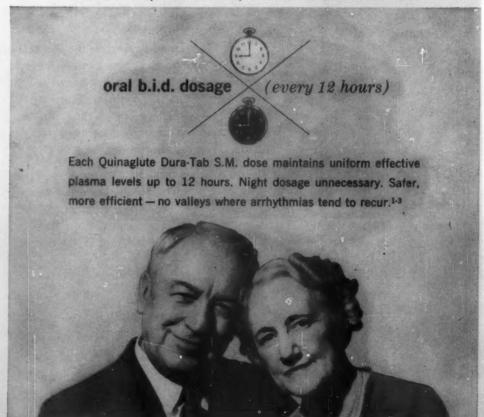
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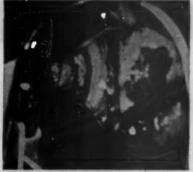
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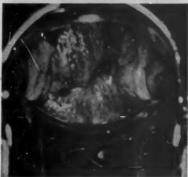
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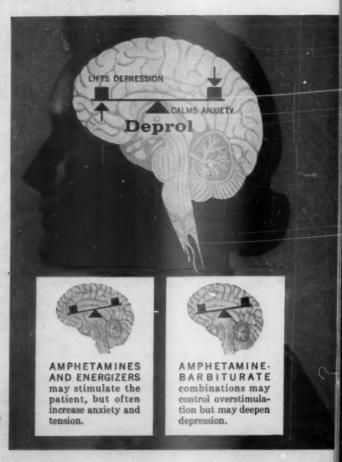
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BIBLIOGRAPHY: 1. Alexander, L.: Chemotherapy of depression—
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Bibliography: 1. Parsons, W. B., Jr., and Flinn, J. H.: A.M.A. Arch. Int. Med. 103:783, 1959. 2. Parsons, W. B., Jr., and Flinn, J. H.: J.A.M.A. 163:234 (Sept. 21) 1957. 3. O'Reilly. P. O.: Canad. M. A. J. 78:402 (March 16) 1958. 4. Altschul, R., and Hoffer, A.: Arch. Biochem. 73:420, 1958. 5. Achor, R. W. P.: Berge, K. G.: Barker, N. W., and McKenzie, R. F.: Circulation 17:497, 1958. 6. Altschul, R., and Hoffer, A.: Circulation 16:499, 1957. 7. Hoffer, A., and Callbeck, M. J.: J. Ment. Sc. 103:310, 1957. 8. Parsons, W. B., Jr., and Flinn, J. H.: Circulation 16:499, 1957. 9. Achor, R. W. P.: Berge, K. G.: Barker, N. W., and McKenzie, B. F.: Circulation 16:499, 1957. 10. O'Reilly, P. O.: Demay, M., and Kotlowski, K.: Arch. Int. Med. 100:797, 1957. 11. deSoldati, L.: Stritzler, G., and Balassanian, S.: Prensa méd. argent. 44:3286 (Nov. 8) 1957. 12. Parsons, W. B., Jr., et al.. Proc. Staff Meet. Mayo Clin. 31:377 (June 27) 1956. 13. Altschul, R; Hoffer, A., and Stephen, J. D.: Arch. Biochem. 54:588, 1955. 14. Seebrell, W. H., and Harris, R. S.: The Vitamins; Chemistry, Physiology, Pathology, New York, Academic Press, 1954, vol. 2, p. 551. 15. Gregory, I.: J. Ment. Sc. 1918. 1918. 1918. Nutrition 6:286, 1957.

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1. Case reports on file, Wyeth Laboratories. 2. Parks, R.V., and Moessner, G.F.: Dual Approach to Patient Care, Scientific Exhibit, A.A.G.P., April, 1959.

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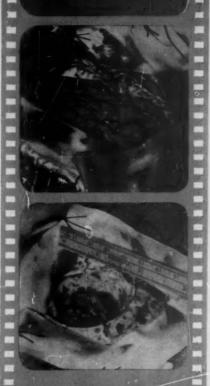
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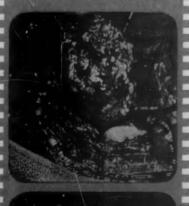
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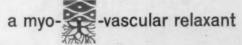
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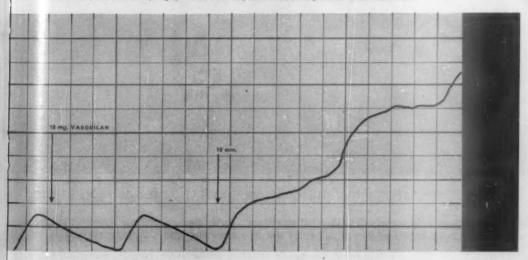
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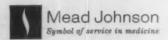
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References: (1) Kaindl, F.; Samuels, S. S.; Selman, D., and Shattel, H.: Angiology 70:165-192 (August) 1959. (2) Kaindl, F.; Pārtan, J., and Polsterer, P.: Wien. klin. Wchnschr. 66:183, 1960. (3) Brücke, F., et al.: Wien. klin. Wchnschr. 66:183, 1960. (4) Nash, C. B.; Drinnon, V., and Clark, B. B.; abstracted, Fed. Proc. 17:397 (March) 1968. (6) Singer, R.: Wien. med. Wchnschr. 107:734-736 (Sept.) 1967. (6) Dungan, K. W., and Lish, P. M.; abstracted, Fed. Proc. 17:386 (March) 1968. (7) Billiottet, J., and Ferrand, J.: Semaine méd. 34:635-637 (May) 1968.

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(hydrochlorothiazide CIBA)

pre-eminently effective whenever diuresis is desired

Indicated in: congestive heart failure ... nephrosis and nephritis ... toxemia of pregnancy ... premenstrual edema ... edema of pregnancy ... steroid-induced edema ... edema of obesity

Supplied: Esidrix Tablets, 25 mg. (pink, scored) and 50 mg. (yellow, scored); bottles of 100 and 1000.







pedal edema reduced with Esidrix

H. K., 44 years old, was admitted to the hospital on 3/3/59 with complaints of swollen abdomen, swelling of both legs and exertional dyspnea. These symptoms had been intensifying over a three-week period. The patient's history included heavy drinking since the age of 18, and one prior admission to the hospital in 1954 with ascites and pedal edema. Diagnosis, at that time, was Laennec's cirrhosis, and the patient responded well to a regimen of diuretics, salt restriction and multivitamins. There was no recurrence up to that leading to his current admission.



Clinical findings worthy of note: Eyes — conjunctivae and sclerae slightly icteric. Chest—diaphragm elevated. Abdomen — girth enlarged, definite fluid wave. Liver palpated 4 fingerbreadths below the costal margin; no other palpable viscera. Extremities—pedal edema (4+).

The patient is well developed and not in acute distress. Blood pressure, 140/80 mm. Hg; pulse, 112/min.; respiration, 20/min. Impression: Laennec's cirrhosis—decompensated.

Treatment: Mercurial diuretic on 3/3 and 3/4, followed by Esidrix, 50 mg. b.i.d., from 3/5 to 3/23 when patient signed out of hospital. Esidrix induced copious diuresis resulting in almost complete disappearance of edema.

New Enzyme-controlled antifungal therapy to meet the growing challenge of Monilial Vaginitis

IN PREGNANCY / IN DIABETES / AFTER ANTIBIOTIC THERAPY—Today, monilial vaginitis is estimated to be a problem in at least 33 per cent of pregnant women and about 10 per cent of nonpregnant females¹—a rapidly increasing incidence attributed partly to the widespread use of antibiotics.

"Vanay" Vaginal Cream broadens the scope of specific therapy: (1) "Vanay" insures a continuous therapeutic fungistatic effect without danger of local reaction; (2) in addition, "Vanay" restores and maintains a physiologic pH and normal vaginal flora—reducing risk of reinfection.

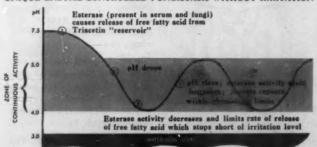
Effective response: Treatment was notably effective in moniliasis, as confirmed by symptomatic relief and post-treatment smears, Assali reports.² Marked clinical improvement was also noted in 154 of 206 patients, and in some cases symptoms subsided within a week of therapy.³

Other advantages: No monilial resistance demonstrated⁴ / prolonged duration of activity⁴ / nonsensitizing / nonirritating / nonstaining / oderless.

"VANAY" Vaginal Cream

BRAND OF TRIACETIN IN NONLIQUEFYING BASE

UNIQUE ENZYME-CONTROLLED FUNGISTASIS WITHOUT IRRITATION3.0





AYERST LABORATORIES
New York 16, N.Y. • Montreal, Canada
9947



Indications: specific in monilial vaginitis...adjunctive in trichomoniasis... also valuable in nonspecific vaginitis where an acid pH must be restored and maintained.

Usual Dosage: 2 to 4 grams daily, Supplied: No. 204-250 mg. Glyceryl triacetate per gram in a nonliquefying base. Combination package: 1½ oz. tube with 15 disposable applicators.

References: 1. Idson, B.: Drug & Cosmetic Industry 84:30 (Jan.) 1959.

2. Assali, N. S.: Personal communication. 3. Combined results of 18 clinical investigators, Medical Records, Ayerst Laboratories. 4. Kubista, R. A., and Derse, P. H.: Antibiotics & Chemotherapy, to be published. 5. Knight, S. G.: J. Invest. Dermat. 28:363 (May) 1957. 6. Knight, S. G.: Antibiotics & Chemotherapy 7:172 (Apr.) 1957.

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Use of the most modern electronic techniques, including transistors and printed circuits, combined with the

craftsmanship of skilled instrument makers of long experience, has not only made possible a superior performing electrocardiograph, but one possessing fine appearance, small size (51/4" x 101/2 x 17"), and low weight-20 pounds.

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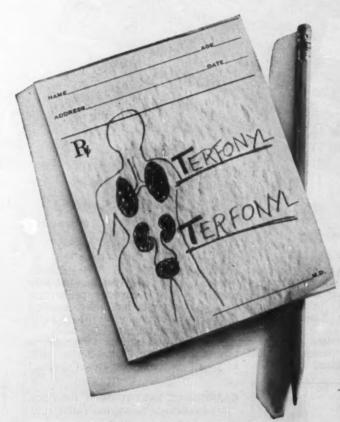
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THE TRIPLE SULFONAMIDE OF CHOICE IN COMMON URINARY, RESPIRATORY, AND OTHER BACTERIAL INFECTIONS



for effectiveness

Prompt, high blood levels1,2 Excellent tissue diffusion³ Broad in scope-attacks both gram-positive and gram-negative pathogens^{2,3}

for safety ...

Highly soluble in urineespecially at critical pH levels Impressively low incidence of sensitization reactions^{2,3} Frequently avoids the problem of the development of resistant organisms

for economy ...

Terfonyl is economical to prescribe for your patients

for palatability ...

Good tasting, raspberryflavored suspension appealing to all age groups—particularly the young and elderly patients

Supply: Raspberry-flavored suspension, containing 0.167 Gm. each of sulfamethazine, sulfadiazine, and sulfamerazine per teaspoonful (5 cc.). Pint bottles.

Tablets, containing 0.167 Gm. each of sulfamethazine, sulfadiazine, and sulfamerazine per 0.5 Gm. tablet. Bottles of 100 and 1000.

Also available: Pentid-Sulfas: Each tablet contains rentid-Suiras: Each tablet contains 200,000 units of crystalline penicillin G potassium and 0.167 Gm. each of sulfamerhazine, sulfadiazine, and sulfamerazine. Bottles of 30, 100 and 500.

References:
1. Campbell, M. F.: Principles of Urology,
Philadelphic, W. B. Saunders Compeny, 1857,
p. 283, 2. Sophian, L. H., Piper, D. L., and
Schneller, G. H.: The Sulfapprinsidines,
New York, A. Colinh, 1852, pp. 70-74.
S. Lekr, D.: New York J. Med. 50:1861
(June 1) 1850,





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first in preference for relief from cough

quiets the cough and calms the patient

Expectorant Antihistaminic

57,

Sedative Topical anesthetic

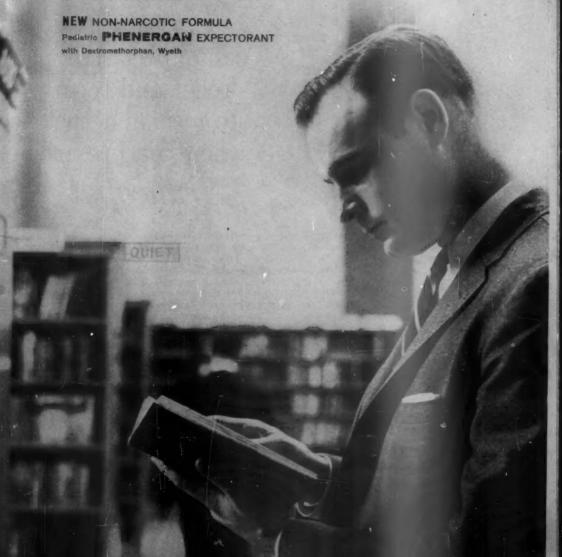
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EXPECTORANT

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Promethazine Expectorant, Wyeth with Codeine Plain (without Codeine)

Philadelphia 1, Pa.





nothing pertinent. The day of the injury he was given Trancopal immediately after the physical examination. Although 100 to 200 mg. three times a day were prescribed, the patient on his own responsibility increased the dosage of Trancopal to 400 mg. three times a day. This dosage was continued for three days and then gradually reduced over a ten day period. During this time, the patient continued to drive his truck.

The muscle spasm was completely controlled and no apparent side effects were noted. For the past six months, the patient has continued to take Trancopal 100 to 200 mg. as needed for muscle spasm, particularly during strenuous days.

Indications - Musculoskeletal: Neck pain (torticollis) / Ankle sprain, tennis elbow / Bursitis / Rheumatoid arthritis / Low back pain (lumbago, etc.) / Fibrositis / Myositis / Osteoarthritis / Postoperative muscle spasm / Disc syndrome. Psychogenic: Dysmenorrhea / Anxiety and tension states / Asthma / Premenstrual tension / Angina pectoris / Alcoholism

New available in two strengths: Trancopal Caplets®, 100 mg. (peach colored, scored), bottles of 100. New strength—Trancopal Caplets, 200 mg. (green colored, scored), bottles of 100. Bosage: Adults, 100 or 200 mg. orally three or four times daily. Relief of symptoms occurs in from fifteen to thirty minu from four to six hours

Irancop

Winthrop LABORATORIES . NEW YORK 18, N.Y.

moving a piano. The pain radiated from the sacral region down to the region of the Achilles tendon on the right side. X-rays for ruptured disc revealed

1. Collective Study, Department of Medical Research, Winthrop Laboratories,

PROVEN EFFECTIVE FOR THE TENSE AND **NERVOUS PATIENT**



66 There is perhaps no other drug introduced in recent years which has had such a broad spectrum of clinical application as has meprobamate.* As a tranquilizer, without an autonomic component in its action, and with a minimum of side effects, meprobamate has met a clinical need in anxiety states and many organic diseases with a tension component.

Krantz, J. C., Jr.: The restless patient - A psychologic and pharmacologic viewpoint. Current M. Digest 25:68, Feb. 1958.

the original meprobamate, discovered and introduced by

WALLACE LABORATORIES, New Brunswick, N. J.

NEW EVIDENCE SUGGESTS ANOTHER REASON FOR PRESCRIBING TAO



UNIQUE "STARBURST" EFFECT: TAO METABOLIZES

The impression that Tao is an unusually active antibiotic has steadily gained recognition by impressive clinical performance. Now come reports of in vivo and in vitro biological and biochemical evaluations that show Tao to be indeed unique. 1.2

Tao differs from other antibiotics in that it is metabolized to multiple active compounds which remain active throughout their presence in the body. There are 7 of these derivatives . . . and all 7 (in addition to Tao) show activity against common Gram-positive pathogens, including resistant strains of Staph, aureus.

In light of these findings, take another look at Tao performance:
• 92% success in published cases of Gram-positive respiratory, skin, soft tissue and genitourinary infection • Effective against 78% of 64 "entibiotic-resistant" epidemic staphylococci. (In the same study, chloramphenicol was active against 52%; erythromycin against only 25% 3 • No side effects in 94%; infrequent reactions mild and easily reversed • Quickly absorbed • Highly palatable.

Sound reasons to: Start with Tao to end 9 out of 10 common Grampositive infections.

Supplisd: TAO Capsules — 250 mg., and 125 mg., bottles of 60. TAO for Oral Suspension — 125 mg. per tsp. (5 cc.) when reconstituted; unusually palatable cherry flavor; 60 cc. bottle. Prescription only.

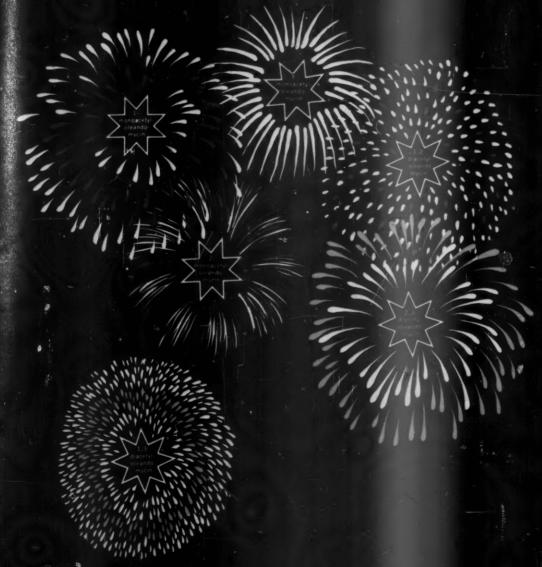
Other TAO forms available: TAO Pediatric Drops: flavorful, easy to administer. TAO®-AC: TAO analgesic, antihistaminic compound. TAOMID®: TAO with triple suifas. Intramuscular er Intraveneus: in clinical emergencies. Prescription only.

 English, A. R., and McBride, T. J.; Proc. Soc. Exper. Blol. & Med. 100:880 (Apr.) 1959.
 Colmer, W. D.; Antibiotics Annual 1955-1959.
 New York, Medical Encyclopedia, Inc., 1959.
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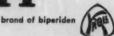
INTO 7 BIOLOGIC MAY ACTIVE DERIVATIVES



New agent for parkinsonism



kineto



PARKINSON'S DISEASE

postencephalitic — idiopathic — arteriosclerotic

DRUG-INDUCED EXTRAPYRAMIDAL DISORDERS

parkinsonism — dyskinesia — akathisia

MUSCULAR SPASTICITY NOT RELATED TO PARKINSONISM

ACTION

Frequently diminshes akinesia, rigidity, and tremor with subsequent improvement in coordinated movement, gait, and posture. Masklike face disappears. Salivation and oily skin are decreased. Oculogyric crises are often lessened in intensity and frequency.

SIDE EFFECTS

Minimum (mainly dry mouth or blurred vision).

DOSAGE

Individual adjustment of dosage is necessary in all instances. Dose range extends from 2 mg. to 24 mg. daily, in divided doses.

AVAILABLE

Supplied as the hydrochloride salt, 2 mg. bisected tablets, bottles of 100 and 1000.

Complete information furnished upon request.

KNOLL PHARMACEUTICAL COMPANY (formerly Bilhuber-Knoll Corp.)

ORANGE NEW JERSEY

In Coronary Insufficiency...

Your high-strung angina patient often expends a "100-yd. dash" worth of cardiac reserve through needless excitement.





Curbs emotion as it boosts coronary blood supply

CONTROL OF EMOTIONAL EXERTION with Miltrate leaves him more freedom for physical activity.

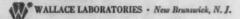
IMPROVED CORONARY BLOOD SUPPLY with Miltrate increases his exercise tolerance.

Miltrate

Miltown® (meprobamate) + PETN

Each tablet contains: 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.
Supplied: Bottles of 50 tablets.

Usual dosage: 1 or 2 tablets q.i.d. before meals and at bedtime. Dosage should be individualized.





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greater antibiotic activity

Milligram for Milligram, DECLOMYCIN exhibits 2 to 4 times the activity of tetracycline against susceptible organisms. (Activity level is the basis of comparison-not quantitative blood levels-since action upon pathogens is the ultimate value.*) Provides significantly higher serum activity level .

with far less antibiotic intake

DECLOMYCIN demonstrates the highest ratio of prolonged activity level to daily milligram intake of any known broad-spectrum antibiotic. Reduction of antibiotic intake reduces likelihood of adverse effect on intestinal mucosa or interaction with contents

unrelenting peak antimicrobial attack

The DECLOMYCIN high activity level is uniquely constant throughout therapy. Eliminates peak-and-valley fluctuation, favoring continuous suppression. Achieved through remarkably greater stability in body fluids, resistance to degradation and a low rate of renal clearance.

•Hirsch, H. A., and Finland, M.: New England J. Med. 260:1099 (May 28) 1959.

ECI.

Demethylchlortetracycline Lederle

of antibiotic design



rum

its.



when emotional turbulence threatens medical or surgical care

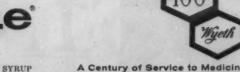
Fear, agitation, and resistance often hinder medical diagnosis and treatment. SPARINE alleviates agitation, overcomes resistance, placates fears.

In addition to calming the patient, SPARINE controls other interfering symptoms: nausea, vomiting, and hiccups. Wyeth Laboratories, Philadelphia 1, Pa.

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Excellent tracings under "IMPOSSIBLE"

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Cardioscribe[®]stability <u>proved</u> a thousand times over

Clinical tests involving 1100 twelve-lead ECGs clearly demonstrated why so many physicians choose G-E Cardioscribe electrocardiograph over price-compromised units, Consistently excellent tracings were reported despite an erratic power supply and with sweltering, 100F room temperatures.

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30 leads without shifting electrodes!

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start...alternate...terminate

with potent, long-acting, intramuscular

Cortrophin the specific, physiologic adrenocortical stimulant

Balance corticosteroid therapy with Cortrophin-Zinc...

After every 6 days' systemic therapy with:

DEXAMETHASONE 4.50-9.0 mg.

METHYLPREDNISOLONE OR TRIAMCINOLONE 24.0-48.0 mg.

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MYDROCORTISONE 150.0-240.0 mg.

CORTISONE 200.0-300.0 mg.

On the 7th day omit the conticosteroid and inject Controphin-Zinc, 40 U.S.P. Units, I.M.

R

nt the systemic corticosteroid ...



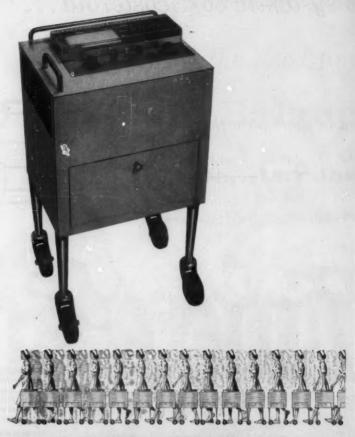
- · Stimulate the adrenal cortex
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CORTROPHIN-ZINC: 40 or 20 U.S.P. units/cc., 5-cc. vials, 1-cc. sterile, disposable syringes. "Produces a more prolonged hormone effect . . . more potent and longer acting than gel ACTH . . . a free flowing substance that can be injected in a very small gauge needle."2

1. Krusius, F. E., and Oka, M.: Ann. Rheumat. Dis. 17:184, 1958. 2. Siegel, S. C.: Lederle Symposium Report, 1:43, 1958.

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A COMPLETE HEART STATION ON WHEELS

with 2 recording speeds . 3 sensitivities . provision for recording other waveforms . provision for visual monitoring

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Model 300 Visitte — only 18 pounds complete, briefcase size. You or your nurse can carry this truly portable instrument anywhere . . . ideal for "on-call" ECG work. Price \$625 delivered, continental U.S.A.

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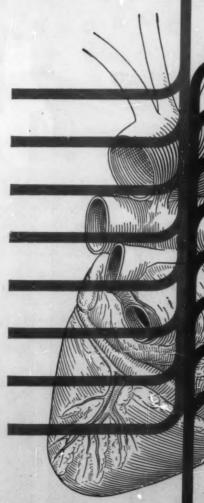
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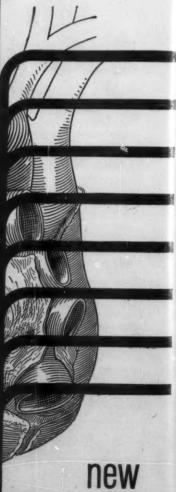
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- prompt, the apeutic hypotenthirom binemia within 36-48 hours^{5,7}
 prolonged, stable effect evenly sustained with single, low, daily dose^{5,7}
- . well tolerated 56.

new approach to the concept of "total management" in angina pectoris





Marplan prevents or reduces anginal pain — Marplan, a new, safer and therapeutically more effective amine oxidase inhibitor, produced "excellent effects with relatively small doses" when used on a continuing dosage schedule in patients with angina pectoris. Indicated primarily for patients with moderately severe to intractable angina pectoris, Marplan often "afforded greater relief than any other compound. . ." Response to Marplan is usually seen in a reduction of the number and severity of attacks, with consequent lowering of nitroglycerin requirements.

A recent Marplan report from the literature²

| Patients | Age | Diagnosis | Usual Dose | Duration of Treatment |
|----------|-----------|---|-----------------|--------------------------|
| 31 | 40's-70's | Angina pectoris. "About one-half were severely ill." | 15-30 mg/day | 1-9 mos. |

Results: "Over 70 per cent of the patients reported notable benefits. . . . "

Marplan creates a more confident mental climate — The profound antidepressive action of Marplan also controls the components of anxiety and hopelessness, which so often aggravate angina pectoris. Patients display a "more cheerful outlook," improving the chances of success of the entire prophylactic regimen.

Marplan strikes a happy balance of potency/safety — Marplan has been tested longer, and in more patients, than any of the recently introduced amine oxidase inhibitors. There have been no reports of liver damage attributable to Marplan or any other serious toxicity. Nevertheless, all precautions set forth in the product literature should be strictly observed. Specifically, since the precise manner in which Marplan improves the cardiac status is as yet undefined and since so many patients attain a virtually painfree state, it is imperative that patients be instructed to maintain the same restrictions of activity in force prior to Marplan therapy.

Supplied: 10-mg tablets in bottles of 100 and 1000.

References: 1. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 2. G. C. Griffith, Clin. Med., 6:1555, 1959.



MARPLAN^{T, H.} —1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine

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capsules make it easier for your overweight patient to maintain a low-calorie diet because they

- · afford relief from the tension and anxiety which so frequently accompany caloric restriction
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When the overweight patient is particularly listless and lethargic-

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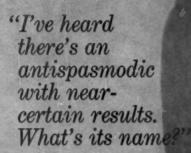
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\$T.M. Reg. U.S. Pat. Off. for dextro-amphetamine sulfate,

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to immediate corticosteroid benefits

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| | TRAUMATIC ARTHRITIS |
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INJECTION



- · ready for use immediately
- · effective immediately

mg. for mg. the most active steroid in true solution

- in joints or soft tissue-direct action at the site of inflammation
- systemically-rapid relief and prolonged effect -complete solubility affords quick diffusion of the therapeutic dose
- needs no reconstitution . . . no refrigeration
- potency up to 40 times that of hydrocortisone
- passes easily through small-bore needles

Injection DECADRON Phosphate can also be used in other joint diseases or soft-tissue conditions such as osteoarthritis, osteochondritis, "trigger" points (localized painful areas in muscles), tendinitis, whiplash injuries (acute), and muscle trauma. Caution: Steroids should not be given in the presence of tuberculosis, chronic nephritis, acute psychosis, peptic ulcer, or ocular herpes simplex.

DOSAGE AND ADMINISTRATION: Injection DECADRON Phosphate is ready for immediate use intramuscularly or intra-articularly. Dosage varies from 4 mg. or less to 20 mg. or more, depending on the nature and severity of the condition.

NOTE: Do not inject into intervertebral joints.

SUPPLIED: 5 cc. vials with 4 mg. dexamethasone 21. phosphate as the disodium salt per cc.

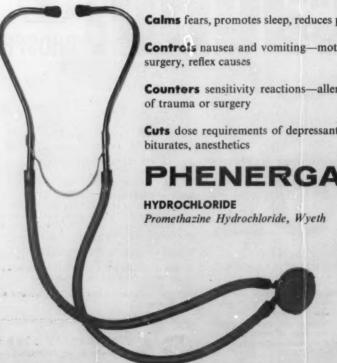
Literature on Injection DECADRON is available at your request.

DECADRON is a trademark of Merck & Co., Inc.



MERCK SHARP & DOHME Division of Merck & Co., Inc., Philadelphia 1, Pa.





Calms fears, promotes sleep, reduces postoperative excitement

Controls nausea and vomiting-motion sickness, pregnancy,

Counters sensitivity reactions—allergy, drugs, tissue edema

Cuts dose requirements of depressant agents—narcotics, bar-

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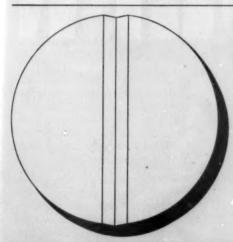
TABLETS SYRUP SUPPOSITORIES INJECTION



GBEATER COUVEUCE

DOUBLE POTENCY

AT LOW COST TO YOUR PATIENT



Pentids 400'

For the treatment of penicillin susceptible infectionsranging from mild to moderately severe-due to hemolytic streptococcus / pneumococcus / staphylococcus / and for the prevention of streptococcal infections where there is a history of rheumatic fever

Clinical effectiveness confirmed by millions of cases Specific in many common infections Daily dosage may be spaced without regard to mealtime Ease of administration with oral penicillin Economy for the patient

SQUIBB



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PENTIDS '400,' each acored tablet con-tains 400,000 units of penicillin G potas-sium buffered, bottles of 12 and 100. Twice the unitage of Pentids 200,000 units.

000 units of buffered penicitiin G potassium per scored tablet, bottles of 12, 100,

PENTIDS FOR SYRUP, 200,000 units of penicillin G potassium per teaspoonful (5 cc.), 12 dose

PENTIDS, CAPSULES, 200,000 units of penicillin G potassium per capsule, bottles of 24, 100, and

PENTIDS SOLUBLE TABLETS, 200,000 units of penicillin & potassium per tablet, vials of 12 and

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High Potency Uricosuric Agent

By significantly increasing renal ANTURAN strikes directly at the

- old tophi

ANTURAN is not designed for the treatment of acute attacks for which Burner brown

after the coronary

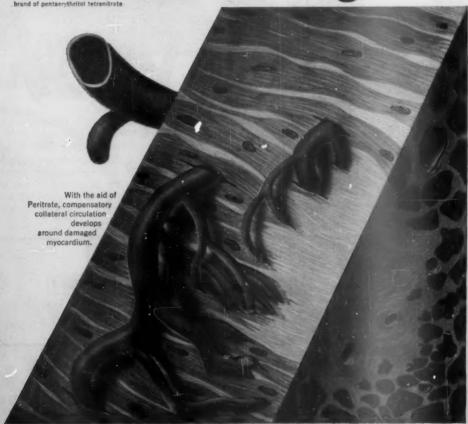
Peritrate improves blood flow ...with no significant drop in blood pressure

Peritrate aids in the establishment of vital collateral circulation in the postcoronary patient.

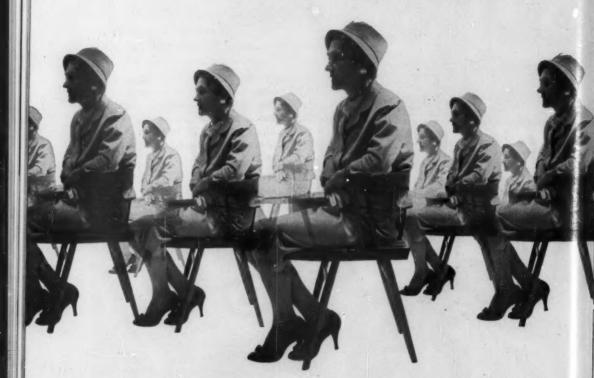


Unlike nitroglycerin, Peritrate is a selective vasodilator that works almost exclusively on coronary vessels with only minimal peripheral effects. It increases coronary blood supply without significant fall in blood pressure or increase in pulse rate. Prescribe Peritrate 20 mg. q.i.d. for your postcoronary patients.

Peritrate 20 mg.



How many patients today complained about pain?



non-narcotic-pain relief equivalent to that of codeine

well tolerated in both acute and prolonged use

wide range of indications-general practice and the specialties

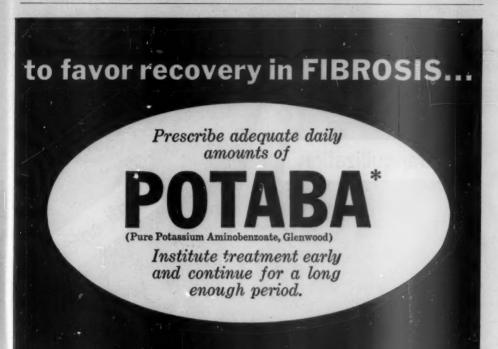
analgesia plus anti-inflammatory action

Supplied: Tablets, bottles of 48. Each tablet contains 75 mg. of ethoheptazine citrate and 325 mg. (5 grains) of acetylsalicylic acid.

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Etheheptazine Citrate with Acetylsalicylic Acid, Wyeth



Evidence obtained from the observations of competent clinical investigators justifies the suggestion that this non-toxic drug may be found of great value wherever the pathological formation of fibrous tissue retards the patient's response to treatment.

Marked improvement in Scleroderma following treatment with POTABA prompted its use in *treatment resistant* Sarcoidosis and Peyronie's disease with the following recently reported results: In 15 cases of Sarcoidosis cough, dyspnea and malaise decreased in 14. Partial or complete clearing of x-ray abnormalities was evident in 13 patients.¹

21 Patients with Peyronie's disease receiving 12 gms. drily in divided doses for periods ranging from 3 months to 2 years responded as follows: Pain, where present disappeared from 16 of 16 cases. Penile deformity improved in 14 of 17 patients. Plaque decreased in 16 of 21.

POTABA DOSAGE FORMS







POWDER, 100 gm., 1 lb., 5 lb.



2 Gram sealed ENVELOPES (100's, 1,000's)



TABLETS of 0.5 gm. 00's, 1.000's)

Complete literature available to ph/sicians on request.

Also available: Information on PASKALIUM (Pure Potassium P.A.S.).

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tranquilization

anti-emetic

greater specificity of tranquilizing action — divorced from such — diffuse — ects as anti-emetic action — explains why

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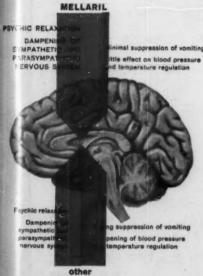
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Thioridazine [MELLARIL] is as effective as the best available phenothiazine, but with appreciably less toxic effects than those demonstrated with other phenothiazines... This drug appears to represent a major addition to the safe and effective treatment of a wide range of psychological disturbances seen daily in the clinics or by the general practitioner."

a new advance in tranquilization: greater specificity of tranquilizing action results in fewer side effects

The presence of a thiomethyl radical (S-CH₃) is unique in Mellaril and could be responsible for the relative absence of side effects and greater specificity of psychotherapeutic action. This is shown clinically by:

A specificity of action on certain brain sites in contrast to the more generalized or "diffuse" action of other phenothiazines. This is evidenced by a lack of appreciable anti-emetic effect.





- 2 Less "spill-over" action to other brain areas hence, absence of undue sedation, drowsiness or autonomic nervous system disturbances.
- 3 A notable absence of extrapyramidal stimulation.
- 4 Lack of impairment of patient's normal drive and energy.
- 5 Virtual freedom from such toxic effects as jaundice, photosensitivity, skin eruptions, blood forming disorders.

| Indication | Usual Starting Dosa | Total Daily Dosage Range |
|--|---------------------|--------------------------|
| ADULTS: Mental and Emotional Disturbances: | | |
| MILD-where anxiety, apprehension and tension are present | 10 mg. t.l.d. | 20-60 mg. |
| MODERATE—where agitation exists in psychoneuroses, alcoholism, intractable pain, senility, etc. | 25 mg. t.i.d. | 50-200 mg. |
| SEVERE—in agitated psychotic states as schizophrenia, manic depressive, toxic psychoses, etc.: | | |
| Ambulatory | 100 mg. t.i.d. | 200 - 400 mg. |
| Hospitalized | 100 mg. t.i.d. | 200-800 mg. |
| CHILDREN: BEHAVIOR PROBLEMS IN CHILDREN | 10 mg. t.i.d. | 20-40 mg. |

Mellaril Tablets, 10 mg., 25 mg., 100 mg.



phenothiazine-type

tranquilizers



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Postgraduate Courses

The following constitutes the three remaining Postgraduate Courses in the Autumn-Winter, 1959-60, schedule:

Course No. 5, CURRENT CONCEPTS OF THE RHEUMATIC DISEASES—THEIR RECOGNITION AND MANAGEMENT: Cornell University Medical College and The Hospital for Special Surgery, New York, N. Y.; Richard H. Freyberg, M.D., F.A.C.P., Director. January 11 to 15, 1960.

Course No. 6, INTERNAL MEDICINE—Selected Subjects: Henry Ford Hospital, Detroit, Mich.; John G. Mateer, M.D., F.A.C.P., Director. January 25 to 29, 1960.

Course No. 7, RECENT ADVANCES IN METABOLIC DISEASES: The Mount Sinai Hospital, New York, N. Y.; Alexander B. Gutman, M.D., F.A.C.P., Director. February 8 to 12, 1960.

The schedule for the Spring, 1960, series is not yet finalized but the following courses are definitely scheduled:

Course No. 1, RECENT ADVANCES IN PHARMACOTHERAPY: University of Washington School of Medicine, Seattle, Wash.; Robert H. Williams, M.D., F.A.C.P., Director. March 21-25, 1960.

Course No. 2, CURRENT CONCEPTS IN CLINICAL GASTROENTEROLOGY: Tulane and Louisiana State Universities Schools of Medicine, New Orleans, La.; G. Gordon McHardy, M.D., F.A.C.P., Director. March 28-31, 1960.

Course No. 3, DERMATOLOGY FOR THE INTERNIST: University of Michigan Medical School, Ann Arbor, Mich.; Arthur C. Curtis, M.D., F.A.C.P., Director. April 25-29, 1960.

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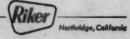
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